DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

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JUL 21 1989

The Honorable Dan Quayle
President of the Senate
Washington, D.C. 20510

EC-1508

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 enacted by Title III of P.L. 99-660, the National Childhood Vaccine Injury Act of 1986, as amended by both P.L. 100-203 and P.L. 100-360.

This report provides information on the implementation of the National Vaccine Program, and discusses the activities planned for Fiscal Year 1989 that are related to the long-term goals of the National Vaccine Plan.

This second report was prepared in consultation with the National Vaccine Advisory Committee, which held its first three meetings in 1988.

Sincerely,

James O. Mason

James O. Mason, M.D., Dr.P.H.
Assistant Secretary for Health,
and Director, National Vaccine Program

Enclosure

OFFICIAL COMMUNICATION
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THE PRESIDENT OF THE SENATE

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NATIONAL VACCINE PLAN

SECOND REPORT TO THE CONGRESS

MAY 1989

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

EXECUTIVE SUMMARY

This Second Annual Report on the implementation of the National Vaccine Program (NVP) and the development of an associated long-range National Vaccine Plan, as required under Subtitle 1 of Title XXI of the Public Health Service Act, provides a summary of the efforts of the NVP's first full year of operation in developing a comprehensive Plan and describes the progress of ongoing program activities. This document was prepared by the NVP in consultation with the National Vaccine Advisory Committee. This report covers the eight major areas addressed in the first report and describes the major activities planned for Fiscal Year 1989 within each of these areas.

Responsibilities of the NVP under Subtitle 2 (National Vaccine Injury Compensation Program) of Title XXI call for a variety of specific activities relating to patient/parent notification, reporting of adverse events associated with immunization, and special studies to be carried out. These activities are also described in this report. Many of these activities are currently underway and are being carried out with existing resources.

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. A summary of AIDS vaccine development is being prepared at the NIH by the National Institute of Allergy and Infectious Diseases (NIAID). Its completion is scheduled for later this year.

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I. BACKGROUND/INTRODUCTION

Subtitle 1 of Title XXI of the Public Health Service Act, enacted by P.L. 99-660, (Appendix 1) as amended by both P.L. 100-203 and P.L. 100-360 establishes a National Vaccine Program (NVP) and calls for the development of a National Vaccine Plan, which is to be submitted to Congress. Subsequent annual reports to Congress serve to update the plan. The Assistant Secretary for Health (ASH) was appointed Director of the NVP. To implement the NVP, the National Vaccine Program Office (NVPO) was created in September 1987 in the Office of the Assistant Secretary for Health, staff were selected, and an NVP Interagency Group (IAG) was created. In addition, the National Vaccine Advisory Committee (NVAC) called for by the legislation was chartered and members were appointed on April 1, 1988.

This document, which is an update of the first vaccine report submitted to the Congress in April 1988, describes 1988 activities of the NVP as well as progress toward the development of a long-term comprehensive National Vaccine Plan. It is clear from the legislation as well as statements by congressional staff that wide input was intended in development of the Plan, particularly from the National Vaccine Advisory Committee. Since being formed, the Committee has held three meetings and has made the development of the Plan its highest priority. Submission of the complete long-term comprehensive National Vaccine Plan to the Congress is projected for early 1990. Consequently, this Report should be read as indicating the major items to be addressed during Fiscal Year 1989 by the National Vaccine Program, one of which is to develop a definitive National Vaccine Plan.

Subtitle 2 of Title XXI, establishing a National Vaccine Injury Compensation Program (NVICP), and related provisions of law mandate 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 alter the sections in the 1989 Report dealing with these three issues. The magnitude of the changes is indicated later in the Report. In October 1988, Dr. Otis R. Bowen, Secretary of Health and Human Services, assigned responsibility for Subtitle 2 compensation activities to the Health Resources and Services Administration (HRSA), a Public Health Service (PHS) agency. As a result the National Vaccine Injury Compensation Program Office (NVICPO) was established in HRSA's Bureau of Health Professions.

II. UPDATE OF THE NATIONAL VACCINE PROGRAM 1988 REPORT TO CONGRESS

During Fiscal Year 1988, many NVP activities were directed toward achieving the eight long-term goals enunciated in the 1988 Report: 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.

This report will give a brief description of the activities to date in these eight areas.

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

AIDS vaccine development is being coordinated by the AIDS Vaccine Research and Development subgroup of the PHS Executive Task Force on AIDS. The NVP collaborates with this subgroup but primarily directs its efforts at non-AIDS vaccines.

The Third Report to Congress in Child Survival by the Agency for International Development (AID), presented to Congress March 1988, summarized the activities and achievements globally against vaccine preventable diseases.

1. Formation and Functioning of the National Vaccine Advisory Committee

Section 2105 of the law requires the establishment of the NVAC and appointment by the NVP Director of members in consultation with the National Academy of Sciences. See Section III. A. of this Report for a description of NVAC activities.

2. Develop a Comprehensive Long-Term National Vaccine Plan

Section 2103 of the law requires the NVP Director to develop a plan to implement NVP responsibilities that cover (a) vaccine research on means to induce human immunity against naturally occurring infectious diseases and to prevent adverse reactions to vaccines; (b) vaccine development, including the techniques needed to produce safe and effective vaccines; (c) safety and efficacy testing of vaccines; (d) licensing of vaccine manufacturers and vaccines by providing for the allocation of resources to support the licensing program; (e) production and procurement of vaccines to ensure that the governmental and nongovernmental production and procurement of safe and effective

vaccines meet the needs of the United States population and fulfill commitments of the United States to prevent human infectious diseases in other countries; (f) distribution and use of vaccines, by providing 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; (g) evaluating the need for and the effectiveness and adverse effects of vaccines and immunization activities; (h) coordination of governmental and nongovernmental activities; and, (i) allocation of supplemental resources to Federal agencies involved in the implementation of the plan for activities not otherwise funded.

See Section III. A. below for information about the development of a long-range National Vaccine Plan.

3. Continue Functioning of the NVP Interagency Group

The IAG, the principal mechanism for coordinating the government-wide implementation of the NVP legislation, held 14 meetings in 1988: January 6, January 27, February 2, February 24, March 8, March 22, April 13, May 17, July 6, August 3, September 7, October 4, November 10 and December 6.

Topics addressed in these meetings included: improving pertussis vaccines, implementation of Subtitle 2 requirements, preparation for NVAC meetings, and preparation of the National Vaccine Plan, among others.

4. Continue Liaison With Other Advisory Groups

Liaison continues with CDC's Immunization Practices Advisory Committee (ACIP), the PHS AIDS Vaccine Research and Development Subgroup and the WHO Executive Board Programme Committee and World Health Assembly.

Various PHS and AID staff continue to participate in meetings of the Committee on Infectious Diseases of the American Academy of Pediatrics, the Task Force on Adult Immunization of the American College of Physicians, the National Advisory Committee on Immunization of Canada, the World Health Organization's (WHO) Expanded Program on Immunization Global and Technical Advisory Group meetings, the Who Scientific Advisory Group of experts on Vaccine Development (SAGE), Technical Advisory Group of the WHO Control for Diarrheal Disease Programme, the Joint Coordinating Board of the World Bank, United Nations Development Programme, WHO-Sponsored Tropical Disease Research Programme (TDR), the Advisory bodies

of the International Center for Diarrheal Disease Research in Bangladesh, WHO Technical Advisory Groups, WHO Expert Committees, and International Tripartite meetings including the FDA equivalents of the U.S., Canada and the United Kingdom.

5. Continue Promotion of Dialogue on Vaccine Policies

At the request of the ACIP, and under the sponsorship of the NVP, the Institute of Medicine (IOM) of the National Academy of Sciences in January 1988 convened an expert committee to evaluate polio vaccine policies in the United States. IOM recommendations include: (1) No change in present policy at this time (primary reliance on OPV with enhanced potency IPV as an acceptable alternative and absolute preference for enhanced potency IPV in immunocompromised individuals and families with members who are immunocompromised); and (2) When enhanced potency IPV combined with DTP is licensed, consideration of a regimen of two or more doses of the combined DTP/IPV followed by DTP and OPV at 18 months and at the time of elementary school entry. An ACIP subcommittee reviewed the IOM material and reported to the ACIP at its fall meeting. The ACIP accepted the IOM Report and agreed with its basic recommendations. The IOM Report is included as Appendix 2.

A workshop on the Status of Acellular Pertussis Vaccine and Swedish Trial Update was held in February 1988. See Section II. G. 1. below.

A workshop was held in September 1988 to assess the progress with alternative measles vaccine strains for use in immunization of infants at less than nine months of age. AID has established a Consultative Group on Vaccine Development with liaison members from WHO and HHS to review its vaccine portfolio policies and directions.

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

The 22nd National Immunization Conference was held in San Antonio, Texas in June 1988. Meetings and lecturers involved the participation of more than 400 public health professionals from national, State and local health facilities involved or interested in childhood and adult immunization.

The 1988 Meeting of the WHO Expanded Program for Immunization (EPI) Global Advisory Group (GAG) met in October 1988 in Abidjan, Ivory Coast. The PAHO Polio Eradication Technical Advisory Group met in Buenos Aires in November 1988. The WHO Technical Advisory Group in Diarrheal Disease Research met in March 1988. The WHO EPI Research Advisory Group met in October 1988. PHS staff were present at each of these meetings.

FDA has consulted with its Vaccine and Related Biologic Products Advisory Committee (VRBPAC) and ad hoc consultants frequently to discuss relevant issues related to the safety and efficacy of new vaccines.

7. Complete a Survey to Inventory Current Vaccine Research

In April 1988 the NVP asked academic, industrial and governmental organizations, known to be interested in biomedical research to develop new and improve existing vaccines, for information about current and projected levels of vaccine research activity. The NVP received more than 80 responses. This baseline profile of research activity will assist the NVP to monitor current vaccine research and development efforts and, in consultation with the National Vaccine Advisory Committee, develop priorities to achieve national goals and describe an optimal use of resources to conduct priority activities. A tabulation of the responses is included as Appendix 3.

8. International Efforts

a. Support for Polio Eradication - PAHO set the goal of elimination of polio from the Americas in 1986. Confirmed cases of polio have fallen to 395 at the end of 1988. In 1988, the World Health Assembly passed a resolution to eradicate polio globally by the year 2000. A global plan was reviewed at the EPI GAG in October 1988. CDC and AID are supporting this effort with technical assistance and resources.

b. Declaration of Measles Elimination from the English-speaking Caribbean - In 1988, the PAHO member States from the English speaking Caribbean established the goal of measles elimination by 1995.

c. Global Immunization Progress - Immunization services were virtually nonexistent in developing countries in 1974. Today, sixty percent of the world's children have received Bacillus Calmette-Guerin (BCG) by their first birthday; sixty percent have received DTP III; sixty-one percent, Polio III; and fifty-five percent measles.

During 1988, HHS and AID signed an agreement with the government of India to undertake a Vaccine Action Program as part of the US-INDIA Science and Technology Initiative. The program supports collaborative vaccine research in both countries directed at the problems of developing countries. AID continued its support for the International Centre for Diarrheal Disease Research in Bangladesh, including oral cholera vaccine trials.

B. ASSURING AN ADEQUATE SUPPLY OF VACCINES

1. Purchase Additional Vaccines for Stockpile

The table below summarizes the status of the stockpile by antigen and by number of weeks' supply at the end of Fiscal Year 1988 and projected for Fiscal Year 1989.

VACCINE	SUPPLY	
	1988	1989
DTP	15.2 weeks	17.0 weeks
MMR	20.8 weeks	20.8 weeks
OPV	20.5 weeks	20.5 weeks
IPV	16.6 weeks	16.6 weeks
DT	20.8 weeks	20.8 weeks
Td	20.8 weeks	20.8 weeks

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

Other vaccines which might be considered included for inclusion are Haemophilus influenzae type b vaccines, pneumococcal polysaccharide vaccine and hepatitis B vaccine. Although CDC contracts have permitted States to purchase pneumococcal vaccine for the past two years fewer than 25,000 doses have been purchased for the target population. Hepatitis B vaccines are not available via CDC contracts; however, the vaccine is readily available from the single licensed manufacturer. Influenza vaccine, although widely used, is not amenable to the stockpile approach since its composition changes each year. These issues will be brought to the NVAC for consideration.

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

The NVAC has begun discussions on this subject.

4. Consider Longer-Term Approaches to Assuring Adequate Supplies

The implementation of the National Childhood Vaccine Injury Compensation Act of 1986, as amended, may encourage additional manufacturers to enter the market. The NVAC has begun discussions on this subject.

C. 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

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

FDA review of preclinical and clinical data (including pre and post marketing data) continues and relevant actions are taken.

b. Maintain and improve national and international surveillance systems for major vaccine-preventable diseases.

Surveillance activities this year included three field investigations of measles outbreaks, involving students at a public four-year college in Durango, Colorado; Amish communities in Lawrence, Indiana; Lebanon County, Pennsylvania; and unvaccinated preschool children and infants in Los Angeles.

A cluster of several cases of flaccid paralysis with onset during August 1987 was investigated. Results indicate that the causative agent was enterovirus 71. This is considered an important investigation since cases had clinical symptoms possibly compatible with paralytic poliomyelitis.

An outbreak of pertussis in Arizona, primarily located in Maricopa County, was investigated. Emphasis was placed on a case-control study looking at risk factors for pertussis and associated knowledge, practices and attitudes related to vaccine usage and disease.

Standardized case definitions for vaccine-preventable diseases were accepted by the Council of State and Territorial Epidemiologists. Standardized definitions, when implemented by the States, will improve the quality of reporting.

Consultation was provided in October 1988 to the Government of Israel during an outbreak of poliomyelitis. The investigations offered the opportunity to evaluate the impact of polio vaccine in preventing disease and impeding spread of wild virus to susceptible individuals.

FDA participated with CDC in monitoring the performance of licensed childhood vaccines in field use conditions. In these collaborative investigations, FDA performed specialized laboratory tests contributing to the elucidation of vaccine efficacy in instances of disease outbreaks in vaccinated high school and college student populations.

CDC is working with developing countries through the Field Epidemiology Training Program to increase epidemiological skills in those countries.

AID is working with 12 African countries to develop surveillance and health information and response capacity through the "Combating Childhood Communicable Diseases/Acute Respiratory Infection" project.

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

FDA continues to evaluate the ELISA methodology for use in diagnosis of pertussis. Studies have been initiated in cloning an antigen which may be useful in the serodiagnosis of pneumococcal disease, i.e., pneumolysin.

In the viral diagnostic area, FDA is also extensively involved in studies evaluating the significance and correlation of standard antibody methodologies (e.g., hemagglutination inhibition and virus neutralization) to newer assay methods such as the ELISA techniques. If validated, the newer techniques, which are more efficient and faster, can replace the older, more cumbersome assays, and be used in epidemiology or vaccine performance studies. These ongoing studies include measles, mumps, rubella and polio viruses.

The NIH continues to support research to develop new and improved diagnostic capabilities for all infectious disease agents. Academic, corporate, and intramural research scientists are involved. Small Business Innovative Research (SBIR) funding is a new resource for work of this nature. Monoclonal antibodies, ELISAs, rDNA probes, and polymerase chain reactions are new techniques being applied. This year a new specific effort was funded to develop diagnostic reagents for enteric viral pathogens.

AID is working to develop rapid diagnostic tests for both epidemiological and clinical use. Studies include emphasis on polio, acute respiratory infection, malaria, diarrheal disease and typhoid. AID has also supported investigation of the epidemiology and etiology of acute respiratory infection in 12 countries through the National Academy of Sciences.

d. Maintain, improve, and establish surveillance systems for adverse events following immunization.

FDA's spontaneous reporting system continues to receive and review adverse reaction reports for vaccines submitted by the private sector, manufacturers and other sources. CDC's Monitoring System for Adverse Events Following Immunization (MSAEFI) receives and reviews reports from the public sector.

FDA and CDC continue to evaluate adverse reaction reports received via the spontaneous reporting system following administration of the Haemophilus b polysaccharide and conjugate vaccines. Reports of disease temporally following immunization resulted in extensive evaluation and additional studies of the Haemophilus b polysaccharide vaccines. Studies have been initiated to monitor events following licensure of the Haemophilus b conjugate vaccines. Post licensure studies to evaluate safety of the polysaccharide vaccines are being conducted by the manufacturers.

CDC's Adverse Events Following Immunization Surveillance Report No. 3 is scheduled for distribution in the second quarter of FY 1989. A survey of opinions of State adverse event personnel concerning MSAEFI and cost was conducted by questionnaire. Analysis is underway.

Contact has been made with other organizations having large linked data bases to determine the practicality of evaluating various events temporally and possibly causally related to vaccination. See also Section III. D. 3. c.

e. Maintain, improve and establish surveillance systems for specific events following the administration of certain vaccines.

Case records of all suspected cases of paralytic poliomyelitis reported with onset during 1987 were evaluated by expert consultants. As a result, five cases of paralytic poliomyelitis, all related to the vaccine, are being officially reported for 1987.

An alternative classification system for cases of paralytic poliomyelitis has been developed. It is based on laboratory and epidemiologic criteria and provides more detailed breakdown of cases and is made possible by improvements in laboratory methods particularly in molecular virology. A manuscript describing the new classification has been accepted by the American Journal of Public Health.

FDA maintains a contract to monitor the possible association between measles immunization and subacute sclerosing panencephalitis (SSPE).

f. Identify other data bases which may be useful in estimating the incidence and severity of vaccine-preventable diseases in the U.S. and abroad. Alternative surveillance for tetanus was undertaken, using National Center for Health Statistics (NCHS) mortality data and State mortality records and case reports. Initial results indicate underreporting of deaths both to the NCHS and the standard CDC morbidity reporting system. This suggests underreporting of tetanus cases to States and to CDC. Further analysis is underway and a paper is being prepared for publication.

AID is continuing its program of demographic and health surveys in developing countries including assessment of immunization status of children and women.

g. Conduct basic, applied, and operational research in the U.S. and elsewhere.

CDC staff participated in the evaluation of the immunization programs and other components of primary health care in Pakistan and Lesotho. CDC also participated in epidemiologic and operational studies and evaluations in several countries in Africa. In addition, AID sponsored CDC and Johns Hopkins University participation in studies in Mexico and Haiti evaluating Edmonston-Zagreb measles vaccine in 6-month-old children.

FDA was another participant in the collaborative study in Mexico providing overall laboratory support utilizing a highly sensitive antibody measurement test (plaque reduction neutralization test, PRNT). In addition, FDA served as the reference laboratory for measuring the potency of measles vaccine used in six independent studies on measles immunization in developing countries, sponsored under the aegis of the WHO.

NIAID staff has assessed emergency room patient utilization of and interest in vaccination. A significant proportion of resistance to use of influenza and pneumococcal vaccines in targeted populations comes from the practicing physician rather than the patient. Furthermore, a substantial proportion of appropriate patients who are offered pneumococcal vaccine in an emergency room setting are ready to accept it.

As an extension of a previous study in Baltimore, FDA participated in a challenge study to determine intestinal immunity following the use of oral poliovirus vaccine or the enhanced potency inactivated poliovirus vaccine. FDA performed serologic assays and conducted an analysis of data from the study.

Basic and applied research on vaccine preventable diseases and vaccines under development is a major effort in FDA biologics laboratories. Special emphasis is given to research involving analysis of the molecular basis of attenuation of the Sabin poliovirus strains with the intent to develop strains of poliovirus devoid of neurotropic potential.

Various laboratories in FDA serve in many capacities as reference laboratories for WHO and PAHO programs. For example, FDA is a reference laboratory for PAHO for the control of yellow fever vaccines produced in the Americas, as well as rabies, diphtheria and tetanus toxoid. FDA also serves as the WHO Collaborating Center for Research on Pertussis Vaccines.

Ongoing research activities are required to ensure the availability of influenza virus vaccines appropriate to the epidemiology of disease. FDA laboratories analyze the antigenicity of new influenza viral isolates collected world wide, and prepare appropriate reagents against these isolates for distribution to manufacturers and other reference and national control laboratories. This research is conducted to provide the most relevant viral antigens for inclusion into vaccines prepared for the upcoming influenza season.

AID is sponsoring research to investigate the optimal formulation of oral polio vaccine. A vaccine efficacy trial of the currently licenced pneumococcal vaccine is being supported in the Gambia to assess its impact on infant mortality secondary to pneumococcal pneumonia. Rotavirus vaccine research is underway in Bangladesh and Venezuela, and low dose hepatitis vaccine research is underway in Baltimore, Maryland. The AID-sponsored new typhoid Vi vaccine has been conjugated and is to be investigated. The oral whole cell with B sub-unit cholera vaccine is to complete its fourth year of efficacy trial in Bangladesh. AID is also sponsoring the development of non-reusable, disposable syringes for use in international immunization programs to reduce the potential risk of the transmission of AIDS during immunization. Indication devices to monitor the cold chain and adequate sterilization are being field tested.

2. Improve Practitioner Awareness

a. Publish information and surveillance summaries in Morbidity and Mortality Weekly Reports and the FDA Drug Bulletin and elsewhere.

Requirements for recording and reporting as described under the Act were published in the MMWR and FDA Drug Bulletin and subsequently in several medical publications. A copy of the requirements was sent to all State Immunization Project Directors, Immunization Public Health Advisors, MSAEFI Coordinators, State and Territorial Epidemiologists and State and Territorial Health Officers.

Nine articles were published in the Morbidity and Mortality Weekly Report including: "ACIP Recommendations for Haemophilus Influenzae Type b Disease;" "Measles in the United States First 26 Weeks 1987;" "ACIP Recommendations for Immunization of Children Infected with HIV;" "Requirements for Permanent Vaccination Records and for Reporting of Selected Events After Vaccination;" "Paralytic Poliomyelitis--Senegal, 1986-1987; Update on the N-IPV Efficacy Study;" "Measles--United States, 1987;" "Mumps in the Workplace--Chicago;" "Progress Toward Achieving the National 1990 Objectives for Immunization;" and "Poliomyelitis--Israel."

Health Information for International Travel, 1988 is now available and being distributed.

AID is working with practitioners through its health communication project in developing countries to increase their awareness of vaccine preventable diseases and to facilitate the incorporation of immunization in their routine practices.

AID is also supporting the American Medical Association for pilot projects with local medical associations in Indonesia and Thailand to involve private practitioners in the delivery of immunization and other child survival services.

b. Update manufacturer's package inserts when indicated. See Section III. C. 3.

Manufacturers' vaccine products package inserts are reviewed for consistency with ACIP recommendations or with Important Information Sheets if one has been prepared for the vaccine addressed by the package insert.

For those vaccine products covered by the National Vaccine Injury Compensation Program (D,T,P,M,M,R, OPV, or IPV, either singly or in combination), package inserts are being reviewed and will be revised consistent with the procedures required by the Act. In addition to publication in the Federal Register, procedures will include discussion with the Advisory Commission on Childhood Vaccines as well as the National Vaccine Advisory Committee.

c. Present surveillance and other data at scientific meetings.

CDC staff presented a review of pertussis cases and epidemiology for 1982-1986 at the Pertussis Symposium, East Berlin, April 1988; at the fourth International Symposium on Pertussis, Copenhagen, September 1988; and at the Interscience Conference on Antimicrobial Agents and Chemotherapy in Los Angeles, October 1988.

Immunization recommendations for international travellers were presented at the International Symposium on Travellers Health, Zurich in May 1988 by CDC staff. Symposium proceedings are to be published.

Preliminary results from the Edmonston-Zagreb measles vaccine trial were presented at the September 1988 Alternative Measles Vaccines Workshop in Washington, D.C.

AID presented progress with global immunization programs at the American Public Health Association Meeting in October 1988 and at the Annual Meeting of the National Council for International Health in May 1988.

d. Continue to work with various advisory groups.

See Section II. A. 4. above.

e. Prepare, update, and distribute "Important Information Statements."

Work proceeds on development of the new Information Statements required by the National Childhood Vaccine Injury Act of 1986, as amended. See Section III. D. 3. a. for more details. These Statements will, among all other things, explain the risks and benefits of those vaccines covered by the National Vaccine Injury Compensation Program. The Vaccine Information Statements are to be given to every person to whom any health care provider intends to administer a covered vaccine. Three draft Statements have been prepared for OPV/IPV, DTP, and MMR. When the review process is completed, draft copies of the proposed vaccine information statements will be

published in the Federal Register. This will begin a 90-day period during which written comments about the vaccine materials are invited from health care providers, parents organizations, and other interested parties. Also a public hearing will be held at CDC approximately 30 days after the publication in the Federal Register.

During 1988, Important Information Statements for DTP, MMR, and Rubella were revised, printed, and distributed to the immunization projects in camera-ready format. For the first time a separate Statement was developed which deals specifically with Td vaccine. A new statement for the Haemophilus influenza b Conjugate vaccine was developed and distributed. The annual influenza statement was revised to reflect changes appropriate for the 1988-1989 flu season and was supplied to immunization projects and to participating HCFA influenza demonstration projects. Camera-ready copy of Chinese, French, Spanish, and Vietnamese translations of the DTP, MMR, and Haemophilus influenzae conjugate statements will be made available to the States.

f. Coordinate various vaccine-preventable disease-related educational programs with private and public organizations.

Five 3-day courses and one 5-day course on Epidemiology, Prevention, and Control of Vaccine Preventable Diseases were conducted in selected locations in the United States.

g. Conduct knowledge, attitudes, and practices survey of health care providers and of the public.

See Section H. 7. below.

The Communication for Child Survival Project conducted "Knowledge-Attitude-Practice" surveys in developing countries with AID support as part of its efforts to promote maternal and child immunization.

h. Prepare prototype educational materials of primary-care physicians and other providers.

Adult immunization materials developed under contract with Abt Associates have been edited, formatted, and duplicated. These materials include a slide presentation which is accompanied by an audiocassette for use with lay and professional audiences. An additional audiocassette provides current information about hepatitis B disease and vaccine use. The packet of material contains a variety of pamphlets in camera ready form and other material including two video tapes discussing adult immunization themes. The "Arm with the Facts" kit was distributed during the fourth quarter of 1988 to immunization programs and other interested parties to provide information and updated material to physicians and the lay public.

An adult immunization slide set of 134 slides has been compiled. It illustrates disease impact, missed opportunities, vaccine usage, and profiles of high risk individuals. The slide set was distributed during the fourth quarter of 1988 to State immunization programs and selected groups for use in making presentations to lay and professional audiences.

i. Prepare prototype manuals for vaccination programs in hospitals, HMOs, and other outpatient settings.

"Immunization Recommendations for Health Care Professionals" has been distributed to immunization projects and other organizations.

3. <u>Improve Public Awareness</u>

a. Prepare and distribute lay publications.

To replenish CDC's exhausted supply of the "Parents Guide to Childhood Immunization," the 1985 Guide was revised and an additional 40,000 copies printed. Each immunization project received 250 printed copies of the Parents Guide and camera-ready copy for their printing needs.

"Questions and Answers Regarding Pertussis and Pertussis Vaccine" continues to be CDC's most frequent mail out when responding to requests for information about the risks and benefits of pertussis immunization.

"A Call to Action" is the adult immunization booklet CDC most frequently supplied in both printed and camera-ready form.

Follow up information on children who were studied in the FDA-sponsored UCLA study of adverse reactions to DTP vaccine was summarized in FDA Consumer Reports, September, 1988.

b. Promote the use of patient education materials and attempt simplification of the "Important Information Statements."

CDC has worked with the American Academy of Pediatrics, Lederle Laboratories, Connaught Laboratories, and Mead Johnson in having these health related organizations include the Important Information Statement material in the AAP Redbook and other physician education publications. The CDC Immunization Division also mails camera-ready copy of the Statements to physicians on request.

c. AID has increased lay awareness of the benefits of immunization internationally by supporting intensive educational and promotional efforts through the Communication for Child Survival project, bilateral projects and support of private voluntary organizations.

D. 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

FDA continues to receive increasing numbers of applications for investigational studies of vaccines (INDs) as well as new product licenses or amendments to licenses for vaccines. New complex technological processes are being used in many of these applications requiring specialized skills in the review. Control activities such as testing, inspections, and monitoring reports of adverse reactions continue.

AID is sponsoring development of an FDA equivalent with the Government of India to enhance the capacity to evaluate new drugs and biologicals, perform controlled testing and ensure quality controls.

2. Assure Prompt Evaluation of New Vaccines

Resources necessary to enable the prompt evaluation of vaccine applications, including monies, staff, and facilities are being identified. Efforts are being made to maintain adequate staffing consistent with the increasing regulatory responsibilities. The Center for Biologics Evaluation and Review (CBER) has expanded its laboratory facilities related to the evaluation of new pertussis vaccines. See Section G. below.

3. Assure Continuation of the Necessary Research Base

The existence of a strong scientific capability to enhance regulatory responsibilities is essential to expedite the review process. Reviewers involved in the vaccine application approval process must have a close familiarity with many scientific disciplines. This is best accomplished by having an active and broad laboratory based research program. FDA's Center for Biologics Evaluation and Review (CBER) has intensified recruitment of scientists to maintain adequate staffing to keep pace with scientific developments and an expanding workload. Research conducted by CBER scientists is made available by publication or presentation at scientific meetings, and is used in FDA regulatory programs.

FDA has been involved in a number of research studies evaluating ways to replace tests in animals by in vitro assays in areas of vaccine control, safety and potency assessment. This research is directed at developing more economical and quantitative assay methods, while at the same time alleviating public concerns about the extensive use of animals in vaccine research and control.

Such studies have been completed for yellow fever vaccine and are in use by the FDA, other national control authorities and by the manufacturers.

Studies to replace the rabies vaccine potency assay (in mice) and the inactivated poliovirus potency assay (in primates) with in vitro methods are under development.

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

The new structure for CBER was published in the Federal Register in March 1988. Selection of staff and training for various scientific programs continues. The reorganization of the Division of Virology has allowed staff to focus on viral vaccines and related manufacturing and safety issues. Other types of immunological agents are now the responsibility of a new Division of Cytokine Biology.

5. Continue Discussion Through Appropriate Channels for New Laboratory Facilities as Requested in the President's Fiscal Year 1989 Budget Request

FDA's FY 1989 request for funding of a new laboratory facility on the NIH campus has been approved by Congress and signed by the President. Monies for construction have been appropriated. Activities related to the planning and construction of the new building are now underway.

E. IMPROVING SURVEILLANCE OF ADVERSE EVENTS

1. Improve Reporting of Adverse Events

a. Information concerning recording and reporting of information as required by the National Childhood Vaccine Injury Act was published in the MMWR and distributed to the entire MMWR mailing list. A section on NVP reporting requirements has been included in each Vaccine Preventable Diseases course.

Reporting has also been stimulated by publication of the mandatory reporting requirements in the FDA Drug Bulletin, and by articles reprinted in the Journal of the American Medical Association.

b. A memorandum from the Director of CDC's Center for Prevention Services and a preprint of the MMWR article were provided to Immunization Project Directors, Immunization Public Health Advisers, MSAEFI Coordinators, State and Territorial Epidemiologists, State and Territorial Health Officers, and Regional Offices. Ongoing consultation is provided to these health officials on interpretation of recording and reporting requirements.

c. Reporting requirements were discussed with all Immunization Project Directors and staff attending the National Immunization Conference in San Antonio in June 1988.

d. CDC's Adverse Events Following Immunization Surveillance Report No. 3 (1985-1986) is scheduled for distribution in the second quarter of FY 1989.

2. Improve Adverse Events Surveillance System

a. CDC surveyed State MSAEFI Coordinators to elicit opinions on the current reporting system, suggestions for improvements, methods to increase reporting, and costs of MSAEFI. Analysis of this information is underway.

b. FDA/CDC cooperation continues. Discussions have taken place between FDA and CDC concerning a single adverse event reporting system to be developed and operated under contract. See Section III. C. 3. c. for further details.

c. The enhanced potency IPV is available to providers. Post-marketing surveillance by FDA and CDC for serious adverse events is continuing.

3. Implement the National Childhood Vaccine Injury Act

This has been completed. See Section III. C for more details.

4. Investigate Additional Approaches for Adverse Event Surveillance

See 5. below.

5. Examine Specific Research Questions

IOM is scheduled to review National Childhood Encephalopathy Study (NCES) data concerning residual neurologic illness following pertussis vaccine in early 1989.

CDC/Vanderbilt Cooperative Studies

A CDC contract to review a Medicaid data base to examine the relationship between neurologic illnesses and vaccination with DTP and measles vaccines is being successfully completed. This effort is also supported in part through an FDA cooperative agreement. Events of interest in the Medicaid population have been identified from 1978 through 1984 and are being linked with immunization histories. Data collection on inpatient events of interest has been completed and work on outpatient events is continuing. A separate study on SIDS and vaccination in this population has been completed and published. Additional funds have been made available to extend the work on vaccine-related adverse events.

Study of Neurologic Illness in Childhood (SONIC)

This study to assess the feasibility of repeating and improving upon the National Childhood Encephalopathy Study (NCES) has progressed satisfactorily. The CDC contract to the University of Washington was awarded in late 1986 and the study began officially in August 1987 after several months of preparation. Surveillance for acute neurologic events and interviews of cases and controls was completed July 31, 1988. Additional funds have been obtained to complete feasibility evaluations, including an assessment of the completeness of reporting from different sources and a survey of immunization coverage in the population. Because the number of cases detected is larger than originally anticipated, the study could provide a sample size large enough to provide additional evidence on the relationship between some acute neurologic events (including febrile seizures lasting 15 minutes or longer and non-febrile seizures) and DTP vaccination.

FDA/Boston Collaborative Study

As part of the FDA cooperative agreement with the Boston Collaborative Drug Surveillance Project, an analysis of data concerning neurological events following DTP vaccine was performed and has been reported (Walker et al, Pediatrics, 1988, 81:345-349).

F. ESTABLISHING RESEARCH PRIORITIES

1. Current Situation

Since the first report to Congress was submitted, research on new vaccines has continued along the lines reported previously. With the efforts to develop an improved vaccine for pertussis and one for AIDS (noted in the first report), the research program continues to conform to the needs and opportunities outlined in the 1985 IOM report, Vaccine Supply and Innovation.

2. Activities During FY 1988 (Excluding AIDS)

a. Reevaluate or Reassess the Institute of Medicine Priorities for Vaccine Research

A reevaluation of the IOM study of vaccine research priorities by NIAID staff suggested the list was reasonably current in identifying priorities based on estimates of the burden of diseases. However, if recent scientific advances in several areas were incorporated in the model, priorities could be slightly rearranged.

An abbreviated version of the IOM study is under consideration in which the disease burden estimates generated previously would be matched to new scientific knowledge.

As directed by the National Vaccine Act, NIAID is negotiating an agreement with the IOM to conduct a literature search on certain adverse reactions associated with whole cell pertussis vaccine and other specified vaccines.

AID continued its support for the International Centre for Diarrheal Disease Research in Bangladesh, including oral cholera vaccine trials.

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

The results of the Swedish trial of two acellular pertussis vaccines showed that the acellular vaccines protect against pertussis but at levels currently thought to be less than desired. Also, results of tests of sera collected in the trial have failed to establish serological correlates,

although all analytical avenues have not yet been exhausted. Interagency cooperation through the NVP Interagency Pertussis Subcommittee continues to drive plans for additional field trials of newer candidate acellular vaccines. The new trials will provide a direct comparison of acellular and whole cell vaccines.

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

The clinical trial in Alaska of one conjugated Hemophilus influenzae type b (Hib) vaccine produced results which were significantly less encouraging than trials of similar vaccines elsewhere. Investigators are comparing the immunogenicity of all available Hib conjugates to determine if the problem is with the vaccine used in the trial or the immune response of the Alaskan native population to the vaccine. Invasive disease caused by Hib continues to be the most serious infectious disease in that population in terms of mortality and serious morbidity, and development of an effective vaccine continues to be a high priority for the Indian Health Service as well as other PHS agencies.

d. Stimulate Basic and Clinical Research on Targeted Vaccines

The vaccine research portfolio of NIAID continues to respond to the priorities identified in the IOM report and to needs and opportunities identified since that report was issued.

AID has established a Consultative Group on Vaccine Development to review its vaccine portfolio, policies and directions in light of the IOM recommendations on priorities for vaccine research for developing countries.

The vaccine research portfolio of AID is based on the IOM report, part II, addressing the needs of developing countries. These priorities have been reviewed by the Agency's Research Advisory Committee and are to be presented to the newly established Consultative Group on Vaccine Development established to oversee the Agency's vaccine portfolio.

e. Stimulate Basic and Clinical Research on Other Important Vaccines

See d) above.

f. Establish Liaison With Members of the Pharmaceutical Industry

FDA continues its close interactions with individual pharmaceutical companies, domestic and international, in their research and development, licensing and post-licensure marketing programs. In addition, FDA has maintained its close interaction with the industry associations.

NIAID staff maintains close contacts with individual vaccine manufacturers. Government and industry scientists work closely in the clinical evaluation of candidate vaccines. This includes performing trials in NIAID contract funded Vaccine Evaluation Units, whose capabilities include testing inactivated and live, attenuated vaccine candidates in all age groups.

g. Complete a Survey to Inventory Current Vaccine Research

An update of the NIAID report on Accelerated Vaccine Development and the AID report on vaccine development are underway. Also, see Section II. C. 7. above.

G. PROMOTING RAPID DEVELOPMENT AND INTRODUCTION OF IMPROVED PERTUSSIS VACCINES

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

The main analysis from the AID sponsored Swedish trial is completed and the results were published in The Lancet on April 30, 1988. The results have been presented to vaccine advisory bodies such as the ACIP and the Committee on Infectious Diseases of the American Academy of Pediatrics (Redbook Committee), and two major meetings have been held (in Stockholm in December 1987 and in Bethesda in 1988) to disseminate the results to the scientific and lay communities in the U.S. and abroad. The transcript of the Bethesda meeting has recently been published. The data generated by the study were of the highest quality.

The major issue remaining is the interpretation of these data. The trial did not include a direct comparison of the acellular pertussis vaccines with the whole cell pertussis vaccine.

2. Test Blood Specimens from Sweden and Correlate Results With Clinical Findings

Serologic results from the Swedish trial have been obtained and presented in the report of the trial in The Lancet. Plans to repeat some of the original serologic work are progressing. An FDA laboratory scientist is scheduled to visit Stockholm to make final testing arrangements.

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

See II. D.

As pertussis vaccine applications arrive at the FDA, they are processed as expeditiously as possible. Samples of products provided by the manufacturer to be considered for clinical use are evaluated in FDA laboratories.

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

At present, acellular pertussis vaccines are undergoing clinical evaluation at Vanderbilt and Marshall Universities. At least four other acellular pertussis vaccines have been proposed for evaluation within NIH Vaccine Evaluation Units (VEU). Two of these vaccines contain only the lymphocytosis promoting factor (LPF), similar to the content of one of the vaccines tested in Sweden. The other vaccines contain combinations of LPF, agglutinogens and/or fimbrial hemagglutinin. The clinical studies in the VEU's are being performed in both infants and children for safety and immunogenicity. Another candidate vaccine is currently being tested for safety and immunogenicity in infants on a large scale basis outside of NIH.

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

Such studies would be expensive and of long duration because of the large number of subjects needed and the low incidence of disease and are therefore not felt to be feasible at this time.

6. Standardize Serologic Tests for Pertussis

The Pertussis Laboratory at the FDA has initiated efforts to carry out this work. The lab has prepared standard pertussis sera which can be made available to other labs for the purpose of comparing lab results. Reagents and methods have been exchanged with Swedish investigators as well as with other investigators and manufacturers. FDA and Swedish serologists have collaborated extensively, including visits to each other's laboratories for closer analysis of methodology.

7. Complete Evaluation of New Diagnostic Tests for Pertussis

New diagnostic tests for pertussis have been developed under CDC contract, including DNA probes and assays to measure secretory IgA and adenylate cyclase in nasal secretions. The sensitivity and specificity of these new tests are being evaluated and the expectation is that these new tests will provide greater sensitivity than is currently possible using culture alone. Further field testing is currently underway. FDA and CDC have collaborated in studies to evaluate serological (ELISA) methods for the diagnosis of disease.

8. Complete Pilot Study of Neurologic Illness in Children

See Section E. 5. above.

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

Ongoing intramural research activities at FDA focus on the identification and characterization of pertussis antigens which might be included in new vaccines. This research includes the development of procedures for purification of antigens, development of laboratory models to study pathogenesis and disease prevention, and procedures to evaluate the immune response. The tools of molecular biology and hybridoma technologies are being used in these studies. NIH sponsors research designed to make use of recombinant DNA techniques to develop and produce antigens suitable for new vaccines. NIH scientists have initiated Phase I studies with a Pertussis toxoid. CDC and FDA laboratories have been involved in the development and evaluation of improved serologic techniques for pertussis.

H. 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

The efforts of the public and private sector to cooperate in the area of childhood immunization range from the use of volunteers in clinic settings to the long standing ties with national organizations. Informal cooperative ventures include the use of hospital auxiliary members and volunteers, together with State and local health staff, who are experienced in the distribution of educational materials in the form of pamphlets and videotape presentations to mothers of newborns and to the parents of elementary and day care students who volunteer to review the immunization status of their children.

More formal involvement with national organizations includes educational efforts and follow up of high risk infants by such groups as the Junior Chamber of Commerce, the American Red Cross, the American Lung Association, and the March of Dimes for specific efforts related to adult immunization. See 3 below.

Internationally, AID is continuing its efforts to expand the capacity of non-governmental organizations and the private sector in the provision of immunization services.

2. Revise Adult Immunization Action Plan

The Division of Immunization, CDC, inaugurated a review of the current adult action plan in conjunction with CDC's Training and Laboratory Program Office in January of 1988. The review process involves the identification of a series of program performance problems which currently face the nation in the area of adult immunization. These problems are then discussed and categorized based on the perceptions of the management group.

After the problems and their perceived causes are enumerated, an action plan is developed to address each of the problems outlined. A summary of the action steps is now being collected. The revised plan will be reviewed by CDC immunization grantees in FY 1989. A separate plan is under development to eliminate Hepatitis B by the year 2015.

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

In January 1988, the Centers for Disease Control, the American Public Health Association, and the National Foundation for Infectious Disease hosted a workshop to outline a combined public and private sector initiative to further the goals of adult immunization in the United States. Further meetings took place during the spring of 1988 which involved representatives of the original three organizations as well as representatives from the American College of Physicians and the American Association of Retired Persons. The meetings resulted in the formation of the National Coalition for Adult Immunization, an informal group of more than 50 organizations and individuals with the common aim of improving the immunization status of adults through the conduct of informational and educational campaigns.

4. Implement Cooperative Agreement for Studying Health Maintenance Organizations

Five HMOs are currently conducting retrospective reviews of their adult ($\geq$ 15 years) members to: determine vaccine coverage with the seven adult antigens; and measure the impact of morbidity and mortality on utilization of services and costs in vaccinated and unvaccinated populations. The results of these studies were presented at the Medical Issues and Data Conference of the American Medical Care and Review Association in January 1989.

The major problems encountered in the study are (1) difficulty in determining vaccination status in outpatient populations, especially in the IPA (Individual Practice Association) model HMO; and (2) cross-referencing vaccination status with disease diagnoses for either inpatients or outpatients.

CDC hopes to develop methods to measure these indicators and views the immunization study as a prototype for evaluation of other HMO cost containment and quality assurance programs.

AID has provided technical assistance in Indonesia to develop and strengthen an HMO to improve health care delivery services. Feasibility studies have also been carried out in several countries including the Philippines.

5. Distribute and Promote Use of Adult Immunization Materials

See Section C. 2. h. above.

National Adult Immunization Awareness Week was held during the last week of October. A press conference was held on October 24, 1988, in conjunction with the Interscience Conference on Antimicrobial Agents and Chemotherapy to promote the activity.

6. Monitor Activities Outlined in Program Grant Guidelines

The May 1987 revision 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 developed 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 are summarized on a quarterly basis and shared with other State and local projects through the "Vaccine Preventable Disease Highlights" and by exchange of ideas during program site visits. 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

The Hawaii State Department of Health and the CDC have completed plans to conduct a survey of physicians in Hawaii to obtain information concerning physicians' knowledge, attitudes, and vaccine usage in the adult population focusing on influenza and pneumococcal vaccines.

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.

Many immunization projects are conducting surveys of hospitals and nursing homes to gather this information. Statewide surveys of nursing homes are evaluating the use of a manual "Managing an Influenza Vaccination Program in the Nursing Home."

Responses have been received from 24 out of 63 projects. In summary, 60 percent of the licensed nursing homes responded. The estimated median vaccine coverage rate for patients in 1987-88 was 83.1 percent. The policy for 74 percent of the nursing homes was to offer influenza vaccine to all residents. Ninety-five percent of the respondents indicated the manual "Managing an Influenza Vaccination Program in the Nursing Home" had not changed their existing influenza immunization policies.

Influenza and pneumococcal vaccine uptake baseline data for adults will be collected using the NCHS Health Interview Survey (HIS) methodology during FY 1989. Discussions concerning the feasibility of including childhood immunization questions on future HIS questionnaires are continuing.

Many projects are now using school and day care immunization records to conduct retrospective immunization level surveys.

AID has conducted numerous baseline and "Knowledge-Attitude-Practice" surveys under the HEALTHCOM Project to improve our understanding of existing immunization and other child survival practices and to develop more effective communications messages to target audiences.

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

Currently underway is the development of profiles on 15 counties that have reported at least five measles cases every year for the past three years or reported more than 50 preschool measles cases over the three year period with more than 30 percent of total cases occurring in the preschool-age group. CDC hopes to identify common factors that contribute to the continuation of measles in these counties and develop better prevention strategies.

Under authority of the Public Health Service Act allowing use of up to 10 percent of grant funding for research purposes, up to $1 million will be made available in Fiscal Year 1989 for cooperative agreements for Immunization Demonstration projects in the areas of immunization assessment and intervention, with special emphasis on inner-city high risk areas.

Ten demonstration grant awards have been made by CDC, in collaboration with the Health Care Financing Administration (HCFA), to test the cost effectiveness of furnishing influenza vaccine under the Medicare program. The first report to Congress is due October 1, 1990. If after two years the coverage under Medicare is cost effective, the demonstration stops and coverage under Medicare becomes effective November 1, 1990. If the coverage under Medicare is not cost-effective or the results are inconclusive, demonstrations continue for another 24 months, or until October 1, 1992. If, at that time, the coverage under Medicare is cost-effective, coverage becomes effective the first day of the first month after the final report is submitted. If found to be cost-effective, 29 million Part B Medicare beneficiaries will be covered. Internationally, AID, through its focus on immunization within its Child Survival Action Program, has sought to identify the reasons for low immunization coverage. Specific attention in A.I.D-supported immunization programs is being given to "missed opportunities", i.e., times when mothers and their infants visit health facilities but are not being immunized. Studies in Peru and Bangladesh are identifying high risk infants and children to target for immunization and other child survival services.

9. Distribute Automated Patient Recall Systems

An automated data system has been developed under contract to assist clinics in patient recall and program management. If costs of the Immunization Control and Evaluation (ICE) system can be reduced, it will be considered for installation in three additional project sites over the next year. Subsequent installations will depend on the successful installation, operation, and maintenance of the program in the four test sites. If successful, ICE should allow programs to assess levels of coverage in preschool populations and assist providers in tracking and follow-up of those shown to be delinquent in immunizations.

10. Review Effectiveness of Preschool Efforts

Preliminary data evaluating the effectiveness of current efforts to vaccinate preschool children including immunization education programs directed at mothers of newborns and active recall systems in public clinics were presented at the National Immunization Conference in June 1988 in San Antonio, Texas.

A new reporting format for vaccine administered in the public sector was approved by the Office of Management and Budget (OMB) and implemented in January 1988. This new format allows better determination of vaccine coverage, age-appropriate administration of vaccine, and estimates of coverage levels in specific age groups. These evaluations will be shared with State and local projects.

11. Convene a National Immunization Conference

The 22nd National Immunization Conference was held June 20-24, 1988. The theme of the Conference stressed the issues, problems, and proposals for improving vaccine coverage in both preschool and adult populations. Almost 400 persons from all 50 states and the District of Columbia participated.

III. UPDATE OF NATIONAL VACCINE PROGRAM (NVP) ACTIVITIES IN 1988

A. FORMATION AND FUNCTIONING OF THE NATIONAL VACCINE ADVISORY COMMITTEE (NVAC)

Since submission of the first National Vaccine Report to the Congress, the National Vaccine Advisory Committee (NVAC) has been established. After consultation with the Institute of Medicine (as called for by the legislation), members were appointed to the NVAC for staggered terms beginning April 1, 1988. The Committee has held three meetings--June 9-10, 1988, September 18-19, 1988, and December 13-14, 1988. Membership on the Committee as well as minutes of the meetings are included as Appendix 4.

The first NVAC meeting, held June 9-10, 1988, focused on presentation by NVAC liaison members of vaccine activities conducted by the agencies coordinated by the NVP: Agency for International Development (AID), Centers for Disease Control (CDC), Department of Defense (DOD), Food and Drug Administration (FDA) and

National Institutes of Health (NIH). The NVAC also discussed the history of public and congressional interest in vaccine research, supply, production and liability; the allocation of resources for the NVP to conduct vaccine activities; defining the NVAC's role and structure; developing strategies to identify vaccine issues; program definition and identification of issues for future NVAC discussions; and stimulation of public and private entities to support immunization as a model for disease prevention.

The second NVAC meeting was held September 19-20, 1988. The National Vaccine Program Interagency Group liaison members presented their recommendations of essential NVP tasks/activities to be included in a long-range, comprehensive National Vaccine Plan, and an analysis of problem areas perceived to be impeding agency work in completing the Plan tasks. Several documents addressing national vaccine policy issues were provided to Committee members.

The Committee decided on seven areas representing the major elements of the National Vaccine Plan. These were: 1) Resources and Funding; 2) Improving Existing Vaccines; 3) Adverse Events; 4) Vaccine Utilization; 5) Vaccine Supply; 6) Vaccine Licensing; and 7) Development of New Vaccines. The NVAC believes that improving existing vaccines and adverse events are overlapping issues. The members felt that the first three issues should receive immediate attention. In addition, it was felt important to draft a Mission Statement for the NVAC and an overall National Vaccine Policy Statement which would serve as the basis for developing the Plan. Committee members formed subgroups to address the development of a vaccine policy statement; the development of a NVAC mission statement; resources and funding; and improving existing vaccines and adverse events.

Under the resources and funding category, the following major subheadings were identified: vaccine supplies; third party payment for immunizations; the excise tax; the role of competition; and domestic and international differences in vaccine prices. Under the category of improving existing vaccines, the following subheadings are being addressed: vaccine field trials; efficacy and safety issues; the limitations of the vaccine market; stimulation of resource development; combination and conjugate vaccines; improvements in the public and private sectors on basic research and development of vaccines as well as the application of new research technologies; and improving public support of vaccine development.

The third NVAC meeting was held December 13-14, 1988. The NVAC discussed and adopted the NVAC Mission Statement and the National Vaccine Policy Statement (Appendixes 5 and 6). The Subgroup on Improving Existing Vaccines met and discussed draft outlines. In connection with the concerns of the two subgroups regarding resources needed to implement NVP activities, the NVAC drafted a letter to Dr. Windom to serve as an end of the year report to the NVP Director. A copy of the letter and Dr. Windom's response to it are included as Appendix 7.

B. NVP INTERAGENCY GROUP (IAG) AND PERTUSSIS SUBCOMMITTEE

In early January, 1988, the NVP IAG and Pertussis Subgroup received draft conclusions and recommendations from the pertussis meeting held in Stockholm in December 1987, and the manuscripts on the Pertussis vaccine trials conducted in Sweden. In addition, the NVP sponsored a pertussis workshop at NIH in February of 1988. The proceedings of the NIH meeting are included as Appendix 8.

Due to the lack of conclusive data on efficacy and the absence of serological correlates of immunity in the Swedish Pertussis Vaccine trial, the IAG and the Pertussis Subcommittee recommended additional clinical trials to compare the efficacy of acellular pertussis vaccines with that of a current whole cell pertussis vaccine. Several countries in Europe--Denmark, Germany, Italy, Sweden, the United Kingdom--and Asia--Japan, Taiwan and Thailand--were identified as potential sites to conduct these trials. The NVP provided resources to allow NVP IAG members from CDC, FDA and NIH to visit potential sites in Denmark, Germany, Italy, Japan, Sweden and the United Kingdom. The NVP also supported a visit to Washington by the Director General of the Ministry of Health of Thailand and representatives of the Children's Hospital of Thailand to discuss with the IAG the possibility of conducting a pertussis vaccine trial in Thailand. The NVP will be providing additional resources for travel by NVP IAG representatives to other countries that may be potential candidates for conducting pertussis vaccine trials.

C. DEVELOPMENT OF YEAR 2000 PREVENTION OBJECTIVES

NVP staff and IAG members participated in the development of Prevention Objectives for the Year 2000 in the area of Immunization and Infectious Diseases.

The NVP Coordinator co-chaired the PHS working group which drafted the objectives. These draft objectives are currently being reviewed by a large panel of expert reviewers outside the PHS and will be modified appropriately before being made available for public comment and final revision. The final objectives will be published in 1990.

D. IMPLEMENTATION OF THE NATIONAL VACCINE INJURY COMPENSATION PROGRAM

1. Formation of the National Vaccine Injury Compensation Office

In October 1988, the Bureau of Health Professions in the Health Resources and Services Administration (HRSA), a component agency of the Public Health Service, was assigned functional responsibility for administering those portions of the National Vaccine Injury Compensation Program (NVICP) concerned with the processing and review of petitions for compensation and advising the Secretary regarding proposed awards. Included in HRSA's responsibilities is oversight of operations of the Advisory Commission on Childhood Vaccines (ACCV). Before formation of the NVICP office, NVP staff prepared letter responses and direct answers to the public on questions about vaccine injury compensation matters and disseminated materials developed by the U.S. Claims Court to persons seeking information about procedures for filing petitions for vaccine injury compensation. The NVP assisted HRSA in its assumption of responsibilities for the new program functions. In addition, NVP and CDC staff briefed HRSA and Department of Justice staff about NVP activities and information about the status of vaccine injury research results.

2. Formation of the Advisory Commission on Childhood Vaccines (ACCV)

The National Vaccine Program Office assisted in the formation of the Advisory Commission on Childhood Vaccines in the following ways: ACCV Charter development; development of Federal Register notices establishing the Commission and seeking nominations for membership on the Commission; preparation of more than 50 letters to professional and public interest organizations, parent groups, vaccine manufacturers and government entities seeking nominations for membership on the Commission; and response to public inquiries about the ACCV functions and membership requirements. The NVICP then took over the task of preparing and submitting to the Secretary a slate of nominees for the Advisory Commission on Childhood Vaccines. The NVP and the NVICP will continue to work closely together.

3. Noncompensation Aspects of the Compensation Program

Responsibility for noncompensation activities described in parts B and C of Subtitle 2 of Title XXI remain with the NVP. These include improvements in licensing, manufacturing, processing, testing, labeling, warning, use instructions, distribution, storage, administration, field surveillance, adverse reaction reporting, vaccine recall, and research in order to reduce the risks of adverse reactions to vaccines.

a. Vaccine Information Statements

The Notice of Proposed Rulemaking of the Vaccine Information Statements required by the National Childhood Vaccine Injury Act is now under final development and review. These Statements will explain the risks and benefits of vaccines covered by the National Vaccine Injury Compensation Program. The Vaccine Information Statements are to be given to every person to whom any health care provider intends to administer a covered

vaccine. Three draft statements have been prepared: Oral Poliovirus and Inactivated Poliovirus (OPV/IPV); Diphtheria, Tetanus, Pertussis (DTP); and Measles, Mumps and Rubella (MMR) vaccines. The proposed vaccine information statements will be published in the Federal Register. This begins a 90-day period during which written comments about the vaccine materials are invited from health care providers, parents organizations, and other interested parties. A public hearing will be held at CDC approximately 30 days after publication in the Federal Register.

b. Reporting Requirements

The law requires mandatory reporting to the Secretary of Health and Human Services of all adverse events associated with certain vaccines normally given to children. The public was formally advised in an April 1, 1988 Federal Register notice and the April 8, 1988 MMWR (included as Appendixes 9 and 10) that as of March 21, 1988, health care providers who administer the specified vaccines and toxoids are required to record permanently certain information and to report certain vaccine-related adverse events, specified in Section 2114 of the law. Providers were advised to direct their reports to either CDC or FDA, depending on whether vaccines were purchased with public or private funds. In addition, FDA provided the same information in the FDA drug bulletin (Appendix 11). Health care providers were also advised of this requirement through their professional journals.

c. Monitoring System for Adverse Events

CDC currently monitors adverse events associated with public sector vaccines and FDA monitors those associated with vaccines purchased with private sector funds.

CDC's currently operating Monitoring System for Adverse Events Following Immunization (MSAEFI) is a consumer-based, stimulated passive surveillance system for adverse events following administration of vaccines purchased with public funds. The system depends on a parent (informed through the information statement) making a connection between the immunization and the adverse event and getting that information to the health department. The event is then investigated and reported to CDC. Approximately 2,000 reports are received each year.

MSAEFI has a variety of objectives. One is to provide data on reporting trends and secular trends in adverse events reporting. The system also has the capacity for evaluating long-term followup of persons reported with adverse events. The system can identify areas for further epidemiologic investigation and research. Limitations of MSAEFI include underreporting, inaccuracies due to reporting and recording by non-medical personnel, the inclusion of events not causally related to immunization, simultaneous administration of multiple vaccine antigens, individual bias in recall, incorrect attribution by the recipient or parent of illness close to the date of vaccination and the lack of background rate data to assess causation.

FDA's spontaneous reporting system, SRS, collects adverse drug and biologic reaction reports and provides information for FDA's post-marketing surveillance of approved drugs and biologics. Since 1969, more than 400,000 reports of adverse reactions have been received and computerized. However, it has only been in the last five years that reports of adverse reactions to biologics have been incorporated into a unified adverse reaction system.

In 1987, of the approximately 54,000 reports received, six percent or approximately 3,500 were for biologics. Of these, 30 percent or approximately 1,000 were for NVP-covered products. Approximately 85 percent of biologic reports are received from the manufacturer rather than directly from health care professionals and consumers.

Data elements from each report are entered into the SRS computerized database after the reported reactions have been described using standardized terminology for later retrieval and analysis. Reports are evaluated for completeness of data elements, to determine whether the reactions were appropriately coded and to add any relevant information to the comments section which will help in assessing the report. Assessments are made as to which reports might warrant further followup based on items such as the severity of the reaction, resulting in hospitalization, disability, or death.

Adverse reaction monitoring provides a profile of the types of reactions that may be occurring to one biologic or a group of biologics. It can also provide information on patient risk factors which may be later investigated in more formal epidemiologic studies.

Limitations to adverse reaction monitoring include inadequate information for assessment, effect on data by other drugs or disease, under reporting, reporting biases and reporting unrepresentative of actual rates of occurrence.

CDC and FDA are currently developing a scope of work to contract for the development of a single system for reporting and evaluating adverse events. Issues associated with current efforts to move towards a single reporting system include determination of a timetable; resolution of differences of how data are collected under the current two systems; reporting criteria; forms design; how reporting will be promoted; routing of reporting; data analyses to be performed; data storage; and type and extent of followup.

d. Special Studies

To comply with sections 312 and 313 of the law, the NVP is to conduct reviews of published technical literature which describe the association between the use of childhood vaccines, especially pertussis and MMR, and certain specified illness and conditions and to study the broad risks associated with vaccines for which injuries are compensable under the law. The responsibility of overseeing this activity has been delegated to the NIH.

The law stipulates that the Institute of Medicine (IOM) be offered the opportunity to conduct the studies so that the most scientifically competent investigators are made available for this activity. The NVP is taking steps to begin this study.

e. Mandate for Safer Childhood Vaccines

To comply with Section 314 of the Act, FDA has been delegated the responsibility to review the warnings, use instructions, and precautionary information presently issued by manufacturers for the vaccines covered by the Compensation Program (diphtheria, measles, mumps, pertussis, poliomyelitis, rubella, tetanus, either singly or in combination) and to determine by rule whether such warnings are adequate. These activities are ongoing.

Section 2128 requires manufacturers to record and report certain information pertinent to the manufacture and control testing of the relevant vaccines. FDA has been delegated the responsibility to assure compliance with this Section; implementing procedures have been initiated.

IV. PLANNED NVP ACTIVITIES FOR 1989

During 1989, NVP activities will continue in the same areas as during 1988 with some modifications of emphasis.

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

Working with the NVAC, NVP staff and IAG members will complete the first National Vaccine Plan and submit it to the Director, NVP, by the end of calendar year 1989. The plan will be a major part of the 1990 Report to Congress.

The IAG (a list of members is included as Appendix 12) will continue to meet regularly and provide the primary vehicle for governmental activities of the NVP. During 1989 more emphasis will be placed on liaison with industry about general issues relating to vaccine development and manufacture. Close liaison currently exists on issues relating to specific vaccines.

B. ASSURING AN ADEQUATE SUPPLY OF VACCINES

Steps will continue to try to exempt vaccines in the vaccine stockpile from payment of the excise tax until they are sold/distributed for use. The number of doses added to the stockpile in 1989 will be dependent on the outcome of this activity.

Longer-term approaches to assuring adequate supplies will be addressed in the National Vaccine Plan.

FDA's control testing will continue to be performed concurrently with the manufacturers to expedite the release of vaccines where needed. FDA will continue to work closely with manufacturers when problems potentially affecting supply are identified.

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

Surveillance systems for vaccine-preventable diseases will be maintained and improved where possible. Surveillance summaries will be published in MMWR and other publications.

The single system for monitoring adverse events following immunization will be implemented during calendar 1989. The vaccine information pamphlets required by PHS Act section 2126 will be completed and put into use.

Recommendations of advisory groups such as the Advisory Committee on Immunization Practices and the Committee on Infectious Diseases of the American Academy of Pediatrics will be published in MMWR and elsewhere. The "Arm with the Facts" kit on adult immunization will be put into widespread use.

D. ASSURING ADEQUATE REGULATORY CAPACITY TO EVALUATE VACCINES

Activities are ongoing to identify appropriate resources to enable the prompt evaluation of new and existing products. These activities include identifying monies, staff and facilities.

Plans for the new CBER laboratory facility will be developed during 1989 and construction will begin in 1990.

E. IMPROVING SURVEILLANCE OF ADVERSE EVENTS

See Section III C. 3. The SONIC will be completed in 1989 and decisions will be made about conducting a full-scale study. Collaborative studies will continue with Vanderbilt and other linked systems for post-marketing surveillance.

F. ESTABLISHING RESEARCH PRIORITIES

Current efforts will continue.

G. PROMOTING RAPID DEVELOPMENT AND INTRODUCTION OF IMPROVED PERTUSSIS VACCINES

Re-testing of serological samples from the Swedish pertussis vaccine field trial will be accomplished. One or more sites will be selected for additional field trials of comparative studies of whole cell pertussis and acellular pertussis vaccines. Development of standardized serologic tests and improved diagnostic tests will continue.

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

The National Vaccine Plan will address the appropriate mix of private and public sector involvement. The National Coalition for Adult Immunization will continue and expand its efforts. Demonstration efforts will be undertaken to develop improved approaches to assuring immunization of inner-city pre-school youngsters. A National Immunization Conference will be held in San Diego in June 1989.

GLOSSARY

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
BCG	- Bacillus Calmette-Guerin
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
HRSA	- Health Resources and Services Administration
HMO	- Health Maintenance Organization
IAG	- National Vaccine Program Interagency Group
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
NCHS	- National Center for Health Statistics
NIAID	- National Institute of Allergy and Infectious Diseases
NICHD	- National Institute of Child Health and Human Development
NIH	- National Institutes of Health
NVAC	- National Vaccine Advisory Committee
NVP	- National Vaccine Program
NVPO	- National Vaccine Program Office
NVICP	- National Vaccine Injury Compensation Program

NVICPO	- National Vaccine Injury Compensation Program Office
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

Appendix 1