AN ASSESSMENT OF THE

CDC Anthrax Vaccine Safety and Efficacy Research Program

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

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Committee to Review the CDC Anthrax Vaccine Safety and Efficacy Research Program

Medical Follow-up Agency

OF THE NATIONAL ACADEMIES

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Willing is not enough; we must do."
—Goethe

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COMMITTEE TO REVIEW THE CDC ANTHRAX VACCINE SAFETY AND EFFICACY RESEARCH PROGRAM

PHILIP S. BRACHMAN (*Chair*), Professor, Department of International Health, Rollins School of Public Health, Emory University

ADAORA ALISE ADIMORA, Assistant Professor of Medicine and Clinical Assistant Professor of Epidemiology, University of North Carolina School of Medicine

SANDRA H. BERRY, Senior Behavioral Scientist and Director, RAND Survey Research Group

TRUDY BUSH,[*] Professor and Director of the Graduate Program in the Department of Epidemiology and Preventive Medicine at the University of Maryland School of Medicine

THEODORE C. EICKHOFF, Professor of Medicine, Division of Infectious Diseases, University of Colorado Health Sciences Center

PATRICIA FERRIERI, Professor of Laboratory Medicine and Pathology and Pediatrics, University of Minnesota Medical School, and Director of the Clinical Microbiology Laboratory at Fairview-University Medical Center

EMIL C. GOTSCHLICH, Vice President for Medical Sciences and R. Gwin Follis-Chevron Professor, The Rockefeller University

MAURICE HILLEMAN, Director, Merck Institute for Vaccinology

DENNIS L. KASPER, Executive Dean for Academic Programs, William Ellery Channing Professor of Medicine, and Professor of Microbiology and Molecular Genetics, Harvard Medical School

MICHAEL D. LOCKSHIN, Director, Barbara Volcker Center for Women and Rheumatic Disease, and Professor of Medicine and Obstetrics-Gynecology, Joan and Sanford I. Weill Medical College of Cornell University

DAVID MADIGAN, Professor of Statistics, Rutgers University

KATHLEEN M. NEUZIL, Assistant Professor of Medicine, Division of Infectious Diseases, University of Washington School of Medicine

N. REGINA RABINOVICH, Director, Malaria Vaccine Initiative, Program for Appropriate Technology in Health (PATH)

BRIAN L. STROM, Professor and Chair, Biostatistics & Epidemiology, University of Pennsylvania School of Medicine

HUGH H. TILSON, Clinical Professor of Epidemiology and Health Policy and Senior Adviser to the Dean, University of North Carolina School of Public Health

Staff

LOIS JOELLENBECK, Senior Program Officer (Study Director since January 2002)
LEE ZWANZIGER, Senior Program Officer (Study Director until January 2002)
JANE DURCH, Consultant (January to May 2002), Senior Program Officer (since June 2002)
KAREN KAZMERZAK, Research Associate
PHILLIP BAILEY, Senior Project Assistant
RICHARD MILLER, Director, Medical Follow-up Agency

[*] Through March 2001.

Preface

Anthrax is a deadly disease, and the organism that causes it, *Bacillus anthracis*, has long been considered a prime agent for biological warfare and bioterrorism. The United States saw its dangers first hand in 2001 when letters containing anthrax spores were mailed to media organizations and to two U.S. senators, resulting in five deaths from inhalational anthrax.

Unlike some biological warfare agents, though, a vaccine is available to prevent anthrax. Anthrax Vaccine Adsorbed (AVA) was licensed in 1970, and until the 1990s it was used primarily to protect veterinarians, textile mill workers who processed imported goat hair, and others with a high risk of occupational exposure to anthrax. Since the Gulf War, however, there has been great concern that U.S. troops deployed to certain parts of the world faced the threat of exposure to biological weapons. In 1998, the Department of Defense began a mandatory anthrax vaccination program intended to protect U.S. forces. Some members of the armed forces have been concerned that the vaccine itself might be responsible for health problems and that the mandatory vaccination program put them at unnecessary risk. Facing concerns over both the need to protect military personnel against the threat of biological weapons and the fears of some about the vaccine, the U.S. Congress directed the Centers for Disease Control and Prevention (CDC) to develop a research program to study the safety and efficacy of the currently available anthrax vaccine. In turn, CDC asked the Institute of Medicine to establish a panel of experts to review the completeness and appropriateness of its research program.

The committee appointed by the Institute of Medicine represented a comprehensive range of professional competencies to be able to successfully evaluate the full scope of the CDC research proposals. CDC provided written materials describing its research program. Over the course of several meetings, the committee also had the opportunity to hear about the evolving research program from CDC investigators and other participating researchers. The committee also heard from military personnel and others with concerns about the safety and efficacy of AVA.

The committee's initial findings and recommendations regarding the CDC research program were presented in an interim report, issued in July 2001. The present report reflects the final results of the committee's detailed deliberations that took into account a final written document describing the entire research program, which was provided to the committee in late February 2002. The committee strongly endorsed certain aspects of the CDC research program, made suggestions for changes in some proposals, and recommended that other planned research activities not be pursued. The committee also found that the bioterrorist events in the autumn of 2001 raised new questions beyond the scope of the original congressional charge and has encouraged CDC to incorporate some additional research into its program.

The committee is aware that the currently licensed vaccine, AVA, could be improved upon and strongly encourages the efforts already under way to develop a new anthrax vaccine. Another Institute of Medicine committee, the Committee to Assess the Safety and Efficacy of the Anthrax Vaccine, has also emphasized the need for a more modern anthrax vaccine and recommended in its March 2002 report that the Department of Defense expedite its work in this area. While reviewing the CDC research program, our committee was alert to the need to address questions concerning the present anthrax vaccine and to consider the contribution that CDC's research might make in support of the evaluation of a newer vaccine.

The committee would like to thank staff members from the Centers for Disease Control and Prevention and their collaborators who prepared reports and presentations for the committee and responded to our questions throughout our deliberations. We especially acknowledge the efforts of Randy Louchart, R.N., M.P.H., who served graciously as the primary contact for the study, and David Ashford, D.V.M., M.P.H., D.Sc.; Deborah Gust, Ph.D.; Laurie Kamimoto, M.D.; Jairam Lingappa, M.D., Ph.D.; Nina Marano, D.V.M., M.P.H.; Stacey Martin, M.Sc.; Michael McNeil, M.D., M.P.H.; Bradley Perkins, M.D.; Conrad Quinn, Ph.D.; and Benjamin Schwartz, M.D.

In addition, the committee extends its thanks to those who provided personal and written testimony to the committee regarding concerns about AVA and the military immunization program.

The early work of the committee was also aided by the contributions of committee member Trudy Bush, Ph.D., M.H.S., of the University of Maryland School of Medicine, who died suddenly in April 2001. Her valuable insights have been missed.

The committee is greatly appreciative of the strong and constant support provided by the study staff from the Institute of Medicine, who worked diligently over the many months of our deliberations and report preparation. Without their excellent and unending support we would never have been able to complete our task. We specifically wish to thank Richard Miller, Lee Zwanziger (study director until January 2002), Lois Joellenbeck, Karen Kazmerzak, Jane Durch, Phillip Bailey, and Pamela Ramey-McCray from the staff of the Medical Follow-up Agency. Other members of the Institute of Medicine and National Academies staff who aided the study include Andrea Cohen, Linda Kilroy, Bronwyn Schrecker, Jennifer Bitticks, Janice Mehler, Sally Stanfield, and Christine Stencel. Jill Shuman assisted in copy editing the report.

Philip S. Brachman
Chair

Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

R. JOHN COLLIER, Harvard Medical School
JAMES W. CURRAN, Rollins School of Public Health, Emory University
BRADLEY N. DOEBBELING, University of Iowa Colleges of Medicine and Public Health
THOMAS R. FLEMING, University of Washington
DOUGLAS T. GOLENBOCK, University of Massachusetts Medical School
MARY GRACE KOVAR, National Opinion Research Center, University of Chicago
MYRON M. LEVINE, School of Medicine, University of Maryland at Baltimore
GEORGES PETER, Brown University School of Medicine
ALEXANDER WALKER, Harvard School of Public Health

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by Morton Swartz, Massachusetts General Hospital, and Paul D. Stolley, School of Medicine, University of Maryland at Baltimore. Appointed by the National Research Council and Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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Abbreviations and Acronyms

ACIP	Advisory Committee on Immunization Practices
AMSA	Army Medical Surveillance Activity
AVA	Anthrax Vaccine Adsorbed
AVIP	Anthrax Vaccine Immunization Program
B. anthracis	*Bacillus anthracis*
BIDR	balanced inventory of desirable responding
BMI	Battelle Memorial Institute
CAMR	Centre for Applied Microbiology and Research
CD4+ T cell	cluster of differentiation antigen 4 T cell
CDC	Centers for Disease Control and Prevention
CFR	*Code of Federal Regulations*
CMI	cell-mediated immune response
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
DMSS	Defense Medical Surveillance System
DNA	deoxyribonucleic acid
DoD	Department of Defense
DTP	diphtheria and tetanus toxoids and pertussis vaccine
EF	edema factor
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunospot
FDA	Food and Drug Administration
GMC	geometric mean concentration
HLA	human leukocyte antigen
HRQoL	health-related quality of life

ICD-9-CM	*International Classification of Diseases, Ninth Revision, Clinical Modification*
ICP	immune correlates of protection
IgG	immunoglobulin gamma
IM	intramuscular
IOM	Institute of Medicine
KAB(s)	knowledge, attitudes, and beliefs
LF	lethal factor
MBPI	Michigan Biologic Products Institute
MDPH	Michigan Department of Public Health
MMF	macrophagic myofasciitis
NCID	National Center for Infectious Diseases, CDC
NHP	nonhuman primate
NIOSH	National Institute for Occupational Safety and Health
NIP	National Immunization Program, CDC
PA	protective antigen
PBMC(s)	peripheral blood mononuclear cells
pXO1	plasmid XO1
pXO2	plasmid XO2
RTI	Research Triangle Institute
SF-36	36-item short-form health survey
SMR	standardized mortality ratio
SQ	subcutaneous
SSA	Social Security Administration
TNA	toxin neutralizing antibody
U.S.	United States
VAERS	Vaccine Adverse Event Reporting System
VHC	Vaccine Healthcare Center
VSD	Vaccine Safety Datalink

Executive Summary

Anthrax is a potentially fatal disease caused by *Bacillus anthracis*, a bacterium that produces spores that are resistant to many environmental conditions and can persist in soils. It is primarily a disease of livestock, and humans have generally become infected through contact with infected animals or contaminated animal products. A vaccine against anthrax, Anthrax Vaccine Adsorbed (AVA),[1] was licensed by the U.S. Food and Drug Administration in 1970. It is currently administered in a series of six subcutaneous doses over an 18-month period and requires annual booster doses.

The stability and availability of *B. anthracis* spores make them a feasible agent for biological warfare, and programs to produce anthrax-based bioweapons are known to exist. In 1998, the Department of Defense (DoD) began a program of mandatory immunization against anthrax for all military personnel. As the program proceeded, however, some military personnel and their families raised concerns about the safety and efficacy of AVA.

Acknowledging both the need to protect military personnel and the concerns about AVA, Congress directed the Centers for Disease Control and Prevention (CDC) to carry out a research program on the safety and efficacy of the anthrax vaccine. The congressional mandate in appropriations legislation for fiscal year 2000 specified that CDC was to address "(1) the risk factors for adverse events, including differences between men and women; (2) determining immunological correlates of protection and documenting vaccine efficacy; and (3) optimizing the vaccination schedule and routes of administration to assure efficacy while minimizing the number of doses required and the occurrence of adverse events."[2] The program has been funded at $18 million annually for fiscal years 2000, 2001, and 2002.[3] In this report, the Institute of Medicine (IOM) Committee to Review the CDC Anthrax Vaccine Safety and Efficacy Research Program reviews the completeness and appropriateness of the research program developed by CDC.

The distribution of anthrax spores through the U.S. postal system in fall 2001 altered perspectives on the risks posed by anthrax and on the need for an anthrax vaccine. This change in context necessarily affected CDC and the committee, which had begun work in October 2000. For example, the domestic bioterrorist events stimulated vigorous government efforts to accelerate the development and licensure of a

[1] As of January 31, 2002, AVA is being manufactured under the name Biothrax.

[2] Conference Report 106-479 to Accompany an Act Making Consolidated Appropriations for the Fiscal Year Ending September 30, 2000, and for Other Purposes, Public Law No. 106-113 (1999).

[3] Conference Report 106-479 to Accompany an Act Making Consolidated Appropriations for the Fiscal Year Ending September 30, 2000, and for Other Purposes, P. L. No. 106-113 (1999); Conference Report 106-645 to Accompany an Act Making Appropriations for the Departments of Labor, Health and Human Services, and Education, and Related Agencies for the Fiscal Year Ending September 30, 2001, and for Other Purposes, P. L. No. 106-554 (2000).

new anthrax vaccine, although it remains uncertain when a new vaccine will be available. In addition, some elements of the research program will be affected by DoD's decision, announced in June 2002, to resume its anthrax vaccination program on a more limited basis than initially planned.

Although beyond CDC's control, some of these factors make the timeline for the CDC research more critical. The results of many of the planned studies will help guide the use of AVA, as well as provide information relevant for the development of a new anthrax vaccine. However, with the push for a new vaccine, some data on AVA could conceivably come too late to be useful. The committee strove to focus on the research questions that exist regardless of these circumstances. The committee also acknowledges that the bioterrorist events have put great demands upon CDC and hopes that this report will provide advice that will help optimize the usefulness of the research program.

STUDY PROCESS

In response to a request from CDC, IOM convened the Committee to Review the CDC Anthrax Vaccine Safety and Efficacy Research Program in fall 2000.[4] The IOM committee members brought expertise in microbiology; infectious diseases; vaccine research, development, and evaluation; postmarketing surveillance of adverse events; regulatory and licensing procedures; epidemiology; biostatistics; survey research and design; immunology; differences in disease between men and women; and health surveillance (see Appendix A for biographical sketches of the committee members).

The committee obtained information about CDC's anthrax vaccine research program from written materials and oral presentations provided by CDC investigators. Military personnel and others with concerns about the safety or efficacy of AVA also made presentations and provided written materials. The committee issued an interim report in July 2001 (IOM, 2001). (See Appendix F for the interim findings and recommendations.) This final report is based primarily on the committee's review of the materials provided by CDC in February 2002, supplemented by information gathered and discussed in the committee meetings. The materials provided in February 2002 describe the objectives and design of the proposed research studies and list critical research questions. (See Box ES-1 for a list of the proposed studies and Appendix C for a subset of the documents provided by CDC.)

The committee made an overall assessment of the CDC research plan (Chapter 7) and reviewed the specific studies proposed by CDC in the three areas of efficacy, safety, and acceptability (Chapters 4, 5, and 6, respectively). The committee also noted additional research needs that became evident following the bioterrorist events of 2001 and expressed concerns about the leadership of the research program (Chapter 7). Key findings and recommendations appear below, and a complete listing appears in Boxes ES-2, ES-3, ES-4, and ES-5.

OVERALL ASSESSMENT OF THE CDC RESEARCH PLAN

CDC considered many of the findings and recommendations in the committee's interim report in the further development of the studies comprising the anthrax vaccine safety and efficacy research program. After examining the components of the research program described in the February 2002 materials, the committee found the CDC response to the congressional mandate to be generally complete and appropriate. The clinical trial is appropriate and satisfactorily designed to address the congressionally mandated charge to optimize the vaccination schedule and the route of vaccine administration. The nonhuman primate (NHP) studies conducted in conjunction with the human clinical trial will largely address the challenge of determining immunologic correlates of protection (ICP) and documenting the efficacy of the vaccine.

[4] The committee was not asked to evaluate the safety and efficacy of AVA. Another IOM committee asked to consider those issues found that AVA as currently administered should be effective against anthrax toxicity from all known strains of the bacterium, as well as from any potential bioengineered strains (IOM, 2002). AVA was also found to be reasonably safe, with reactions occurring soon after vaccination that are comparable to those observed with other vaccines regularly administered to adults. (See Appendix G for the findings and recommendations from that committee's report.)

BOX ES-1
Studies Proposed by CDC for the Anthrax Vaccine Safety and Efficacy Research Program

Efficacy

- Anthrax Vaccine Adsorbed: Human Reactogenicity and Immunogenicity Trial to Address Change in Route of Administration and Dose Reduction
- Nonhuman Primate Vaccine Dose Ranging, Immunogenicity, and Challenge Trial
- Immune Correlates of Protection (ICP) Against Inhalational Anthrax

Safety

- Anthrax Vaccine Adsorbed: Human Reactogenicity and Immunogenicity Trial to Address Change in Route of Administration and Dose Reduction
- Follow-up Study of Textile Mill Workers Vaccinated Against Anthrax
- Studies Based in the Vaccine Healthcare Center Network
  - Effects of Change of Route of Administration on Local Adverse Events Following AVA Vaccination
  - Effect of AVA Vaccination on Health-Related Quality of Life
  - Effect of Hormonal Phase in the Female Population on the Occurrence of Adverse Events Following Immunization with AVA
- Enhanced Signal Detection and Hypothesis Testing for Adverse Events Following Anthrax Vaccination
- Possible Role of Aluminum Hydroxide Adjuvant in AVA-Associated Adverse Events

Acceptability

- Survey of Knowledge, Attitudes, and Beliefs Regarding the Anthrax Vaccine Among Military Personnel
- Survey of Civilian and Military Health Care Providers Regarding the Anthrax Vaccine and the Reporting of Possible Vaccine-Associated Adverse Events

The committee's qualifications regarding the research plan arise from both the lack of passive protection studies in the determination of ICPs (discussed in Chapter 4 and reviewed briefly below) and potential constraints from small sample sizes in the investigation of differences between men and women in risk factors for adverse events that occur at the time of vaccination (described in Chapter 5 and recapitulated below). Although the research program lacks satisfactory plans for investigating possible adverse health effects that are rare or might become evident many years after vaccination, the committee has seen no evidence that such studies should be a high priority. These limitations do not alter the committee's conclusion that the CDC research program as planned includes most of the studies needed to provide a strong and appropriate response to the congressional mandate.

When considered in its entirety, however, the CDC anthrax vaccine research program also includes elements that the committee considers to be of lower priority and some that should not be carried out as planned.

Findings:

1. With respect to the tasks specifically outlined in the congressional mandate, CDC's research response is generally complete and appropriate.

2. When considered as a whole, however, the research program has elements that are of low priority and other elements that are inappropriate and should not be carried out as planned.

PROPOSED STUDIES ON THE EFFICACY OF THE ANTHRAX VACCINE

Anthrax Vaccine Adsorbed: Human Reactogenicity and Immunogenicity Trial to Address Change in Route of Administration and Dose Reduction (Human Clinical Trial)

CDC is conducting a human clinical trial with 1,560 healthy civilian volunteers to compare the immunogenicity of subcutaneous (SQ) and intramuscular (IM) administration of AVA, and the immunogenicity of the licensed schedule of six SQ doses and annual boosters with regimens that use fewer doses administered IM. The committee found that the study, as described in the protocol, provides an appropriate basis for these intended comparisons, which will help optimize the administration of AVA. In conjunction with the NHP challenge studies, this study should also provide information on the kinetics of the antibody response, which is valuable for the development and licensure of new anthrax vaccines. These research needs were emphasized in another IOM report on AVA (IOM, 2002), and their importance has increased as a result of the bioterrorist incidents in fall 2001.

Finding: As described in the study protocol, the human clinical trial is generally responsive to the congressional mandate and to important research needs for determining immunologic correlates of protection, documenting the immunogenicity of AVA, and optimizing the vaccination schedule and routes of administration of AVA.

Nonhuman Primate Vaccine Dose Ranging, Immunogenicity, and Challenge Trial

This study will test the efficacy of AVA in protecting NHPs (i.e., rhesus macaques) when they are exposed to aerosolized doses of anthrax spores. It is an appropriate and crucial aspect of the congressionally mandated research to document the efficacy of AVA and to determine immune correlates of protection. Because challenging humans with lethal agents such as *B. anthracis* is not ethical, animal experiments are necessary, and the rhesus macaque is an appropriate model for such studies (IOM, 2002). The current approach to the NHP study promises to meet the need for additional information about protective levels of antibody or other immune factors. Such information can be useful not only in optimizing the schedule of doses for AVA, but also in evaluating the efficacy of new anthrax vaccines under development.

Finding: The committee finds that the nonhuman primate studies that have been proposed as a means to provide information about the efficacy of AVA are well designed and responsive to the congressional mandate and to important research needs. The information gathered will inform and influence the development and licensure of new protective antigen-based anthrax vaccines.

The research protocols and other materials submitted to the committee for review do not, however, describe plans for passive protection studies. Passive protection studies are experiments in which serum from immunized animals or humans (i.e., immunoglobulin) is administered to naïve animals, who are then challenged (by exposure to anthrax spores in studies of AVA) to evaluate the level of protection provided by the circulating antibody in the immunized animal or human. The committee considers passive protection studies to be an essential component of a research program on AVA (see Chapter 4).

Recommendation: CDC should conduct passive protection studies as part of its anthrax vaccine safety and efficacy research program.

The bioterrorist incidents in fall 2001 made clear the need for additional information about the protection afforded by AVA against exposure to different amounts of *B. anthracis* spores. The committee urges CDC to help address this research gap. The recommended passive protection studies will help determine an optimal level of antibody or other component of immunity to achieve protection against a

given dose of spores. Once a protective level of antibody (or other correlate of protection) has been established, the effect of varying the size of the challenge dose should be evaluated.

Recommendation: CDC should support or conduct research on the effect of the size of the challenge dose on immunity provided by vaccination with AVA.

Immune Correlates of Protection Against Inhalational Anthrax Studies

While qualitative correlations between survival and the presence of antibodies to protective antigen (PA)—a protein produced by *B. anthracis* and the principal immunogen in AVA—have been established in animal models, quantitative correlations remain to be determined. In general, the committee found that the planned ICP studies should provide the additional information needed to make these quantitative correlations. This information can be useful for better understanding AVA's mechanism of protection and also for licensing newer PA-based vaccines that are under development.

However, CDC's many goals for the ICP studies varied widely in scientific value. Quantifying and characterizing the humoral responses to PA and other anthrax antigens are important and necessary goals, but the committee considers it unlikely that the analyses in support of CDC's other goals will provide important new insights regarding the mechanism by which AVA protects against anthrax infection.

The committee also had concerns about the plans to carry out multiple lymph node biopsies, bone marrow biopsies, and bronchoalveolar lavage on a subset of rhesus macaques included in the NHP studies. Researchers hope to use those samples for tests to correlate immune responses occurring in tissues or organs of the macaques with the animals' peripheral blood mononuclear cells. According to the protocol, the analysis may provide new guidelines for the minimum number of vaccinations necessary to generate long-term humoral immunity to anthrax. The committee questions the extent to which these studies can contribute to addressing this research question. In addition, the procedures do not appear to be adequately justified or even likely to be useful, since the frequent administration of anesthesia and the repeated biopsies may alter the responses of interest. The proposed research is descriptive, rather than hypothesis-driven, and should be a low priority.

Recommendation: On the basis of the information provided to the committee for evaluation, the committee recommends that the NHP studies requiring multiple samplings from biopsies of lymph nodes and bone marrow and from bronchoalveolar lavage should not be continued in their current form. If such studies can be adequately justified, they should be modified to require fewer invasive procedures.

Finding: With the exception of the biopsy and bronchoalveolar lavage studies noted above, the committee finds that the ICP studies that have been proposed as a means to provide information about the efficacy and immunogenicity of AVA are responsive to the congressional mandate and to important research needs. The information gathered will inform and influence the development and licensure of new PA-based anthrax vaccines.

PROPOSED STUDIES ON THE SAFETY OF THE ANTHRAX VACCINE

Human Clinical Trial

The committee concluded that the human clinical trial should provide helpful information about the risk factors for common adverse reactions that occur soon after vaccination, including differences in reaction rates related to SQ versus IM administration of AVA. It should also be possible to examine differences between men and women in the occurrence of immediate-onset adverse events and to compare those results with findings from other studies (CDC, 2000; Hoffman et al., submitted for publication; Pittman et al., 2002). However, additional studies beyond those described by CDC would be needed to better understand the reasons for any differences between men and women in the occurrence of adverse

events. The committee cautions that if used by itself, the SF-36 health status survey is unlikely to be a satisfactory tool for the proposed evaluation of changes in health-related quality of life associated with AVA vaccination.

Finding: As described in the study protocol, the human clinical trial is generally responsive to the congressional mandate to evaluate the incidence of, risk factors for, and differences between men and women in local and systemic immediate-onset health effects associated with AVA and the effect of the route of vaccine administration on adverse events. The study will also provide a 42-month follow-up period during which to monitor the occurrence of later-onset health effects.[5]

Follow-up Study of Textile Mill Workers Vaccinated Against Anthrax

The committee recommends against the retrospective cohort study intended to investigate potential chronic health effects or later-onset adverse events following anthrax vaccination. As proposed, the study of former textile mill workers is highly unlikely to be able to detect important later-onset health effects of anthrax vaccination that might exist and would carry the risk of producing spurious positive or negative associations. The study faces these problems because of the difficulty in finding truly comparable control groups and because of the relatively small size of the study population and the large number of variables in the planned analyses. Conducting the study poses the risk of generating unwarranted health concerns among the participants, without scientific benefit.

Recommendation: CDC should not continue work on the proposed follow-up study of textile mill workers who received AVA.

Studies Based in the Vaccine Healthcare Center Network

The Vaccine Healthcare Center (VHC) Network is a collaboration between DoD and CDC to address issues of safety and acceptability of all types of vaccines administered within the military health care system. The VHC network is expected to serve as a base for research on AVA and other vaccines administered to military personnel. The committee reviewed draft proposals for studies of (1) the effect of route of AVA administration on the occurrence of adverse events soon after vaccination; (2) the effect of AVA on health-related quality of life; and (3) the effect of women's hormonal phase on the occurrence of adverse events.

The first of these proposed studies could provide useful postmarketing-type data to confirm the rates of adverse events observed in the human clinical trial, if the study population is comparable in size to that of the clinical trial. The study, however, is not suitable for monitoring a large study population (10,000 subjects) to detect the occurrence of less common, medically significant conditions that may not be seen during a clinical trial.

Recommendation: A VHC-based study to verify reaction rates to AVA and the validity of self-reported data observed in the clinical trial should provide for intensive active surveillance of relatively small cohorts, similar in size to the study groups in the human clinical trial.

Because of questions about its feasibility, the committee recommends against the second VHC study, designed to compare the effect of SQ versus IM administration of AVA on health-related quality of life using the SF-36 health survey. This study is likely to face the following difficulties: distinguishing differences between generally healthy populations with the SF-36, following study participants who have been

[5] The committee has adopted the terminology used by the Committee to Assess the Safety and Efficacy of the Anthrax Vaccine (IOM, 2002). The phrases "short term" and "long term" were not used to characterize adverse events because of the potential for confusion. Instead, the duration of an adverse event is characterized as acute or chronic; the timing of the onset of an adverse event is characterized as immediate or later.

deployed, and distinguishing any effects on health status related to receiving AVA from those related to deployment or to receiving other medications and vaccines in preparation for deployment.

The proposed study about the effect of women's hormonal phase on the occurrence of adverse events is likely to prove more complex than is suggested by the proposal because of the many potentially confounding factors (e.g., age, race, parity, and contraceptive use). The committee considers the study a low priority.

The committee concluded that the complexities evident in the three draft proposals for VHC-based research studies indicate the need for regular consultation with a standing panel of outside scientific experts for guidance on matters ranging from study design to data analysis for all VHC-based research activities.

Recommendation: An external scientific advisory group should be constituted to provide guidance to CDC and DoD on all research undertaken through the VHC network. Given the draft study proposals reviewed by the committee, the advisory group should include, among others, experts in biostatistics (propensity analysis), health care outcomes assessment, pharmacoepidemiology (postmarketing surveillance), and clinical epidemiology (medically unexplained symptoms).

Enhanced Signal Detection and Hypothesis Testing for Adverse Events Following Anthrax Vaccination

The committee is pleased to see that CDC has begun to give attention to the Defense Medical Surveillance System (DMSS)—a set of DoD-wide health-related databases covering military personnel on active duty—as a resource for generating and testing hypotheses concerning adverse events that might be associated with receipt of AVA. In particular, data from DMSS should be used to follow up hypotheses concerning AVA that have already been generated. To allow for analysis of health effects of AVA that might arise beyond the period of active duty, CDC should investigate ways to use DMSS data in conjunction with morbidity and mortality data from ongoing military cohort studies, such as the Millennium Cohort Study,[6] and from the health system of the Department of Veterans Affairs.

The committee is concerned, however, about the proposed use of data mining to screen data from the Vaccine Adverse Event Reporting System (VAERS), a spontaneous reporting system that is inherently incomplete and subject to often-unknown reporting biases. Such techniques must first be thoroughly evaluated in other, more complete data sets—possibly DMSS—and shown to be effective even in the face of the kinds of biases inherent in the VAERS data. The availability of data on health outcomes following exposure to AVA in both DMSS and VAERS may provide an opportunity to use associations identified in DMSS in efforts to validate the use of data mining in VAERS.

Recommendation: Hypothesis generation using data mining and other statistical techniques for screening data should be tested and validated in DMSS or other structured data sets before being considered for use with VAERS. Only if these techniques can be validated with a structured data set and then with VAERS data should they be used to generate hypotheses from VAERS concerning adverse events and AVA.

Despite indications of greater collaboration between CDC and DoD on the analysis of DMSS data, the committee is concerned that as of February 2002, these studies were still not receiving the appropriate attention, priority, and funding. The committee also sees a need for an overall plan to guide the hypothesis-generation and hypothesis-testing activities, with staff designated to provide overall management and an external panel to provide periodic advice on analyses.

[6] The Millennium Cohort Study will monitor a total of 140,000 U.S. military personnel during and after their military service for up to 21 years to evaluate the health risks of military deployment, military occupations, and general military service (see http://www.millenniumcohort.org/about.html).

Recommendation: Adequate resources (substantially more than can currently be identified from the CDC–DoD Memorandum of Understanding) should be made available to support the use of DMSS data for testing hypotheses regarding health effects related to AVA or other vaccine exposures.

Possible Role of Aluminum Hydroxide Adjuvant in AVA-Associated Adverse Events

The committee concluded that studying the possible role of aluminum hydroxide in adverse events would be difficult and is not of sufficient priority to pursue as part of the CDC anthrax vaccine research program.

PROPOSED STUDIES ON THE ACCEPTABILITY OF THE ANTHRAX VACCINE

Investigation of the acceptability of the anthrax vaccine was not directly specified in the congressional mandate to CDC, but acceptability issues are potentially important in the overall success of any vaccination program. The committee found the planned survey of knowledge, attitudes, and beliefs (KABs) regarding the anthrax vaccine among 17,000 members of the military to be unnecessary in its proposed form. However, information about attitudes in groups that are likely to be immunized can help guide the development of educational interventions intended to address concerns about the anthrax vaccine. Thus, the committee recommended against exhaustively detailing the level of concern among various segments of the military population. Instead, relevant information could be gathered using focus groups and smaller surveys and then applied to the development, refinement, and evaluation of educational interventions.

Recommendation: In view of the study timeline and research needs, CDC should modify the design of the KAB study of military personnel to focus on more timely development of educational interventions and the evaluation of their impact on the acceptability of AVA and a broader range of vaccines, including a new anthrax vaccine.

The committee also felt that the separate survey of health care providers could be of greater value if the focus was broadened from providers' KABs about VAERS and AVA to their KABs about immunization and adverse events more generally. The committee advises including not only health care providers who administer vaccines, but also those who might see patients with concerns about adverse events. Thus, while the study as proposed is considered of low priority, it could make a more important contribution to the research effort if it were modified.

Recommendation: In addition to gathering information on KABs about VAERS and the current anthrax vaccine, CDC should modify the survey of health care providers to study KABs about a new anthrax vaccine, other military vaccines, and vaccines in general, with a focus on information useful for timely development and testing of appropriate educational materials. The study population should include health care providers who may treat service members with adverse events following vaccination, as well as those who administer vaccines.

RESEARCH GAPS

The gaps in the CDC research program that were noted in the preceding discussion of the individual research studies are summarized in Table ES-1.

TABLE ES-1 Additional Research Needs Concerning the Safety and Efficacy of the Anthrax Vaccine, Identified and Prioritized by the Committee

Committee Priority	Additional Research Needs Identified by the Committee
High	Passive protection studies in nonhuman primates (Chapter 4, p. 51)
	Studies of the effect of the size of the challenge dose on protection (Chapter 4, p. 51)
	Linkage of the Defense Medical Surveillance System and other databases for longer-term follow-up of military personnel who received AVA (Chapter 5, p. 77)
Medium	Focused, small-scale surveys of knowledge, attitudes, and beliefs regarding the anthrax vaccine among military personnel to guide the design of information programs (Chapter 6, p. 87)
	Survey of civilian and military health care providers regarding vaccination and the reporting of possible vaccine-associated adverse events (modification of a study proposed by CDC, Chapter 6, p. 89)

BIOTERRORISM AND RESEARCH NEEDS

CDC's research program was mandated by Congress in 1999 and initiated before the distribution of anthrax spores in fall 2001 resulted in five deaths from inhalational anthrax and the possible exposure of more than 30,000 people to the risk of infection (CDC, 2001a,b). The nation's experience of civilian bioterrorism confirmed the urgency of the research that CDC has already planned, and it also showed the need for studies related to the possible use of anthrax vaccine following exposure to anthrax spores and its use in the civilian population. With some additions to its research portfolio, CDC could help respond to these other research needs.

In particular, the CDC research plan could benefit from the addition of studies using animal models to investigate the immunogenicity of AVA (or another anthrax vaccine) when it is administered following, rather than before, exposure to anthrax spores. Because it is not ethical to expose humans to anthrax spores for research purposes, studies of postexposure use of the anthrax vaccine must be conducted in animals. Only two such studies have been carried out in nonhuman primates. This research is also needed to establish the appropriate duration of antibiotic prophylaxis after vaccine administration (IOM, 2002).

Recommendation: As part of its research plan, CDC should support studies in laboratory animals to establish an appropriate duration for antibiotic prophylaxis when administered with AVA following *B. anthracis* spore challenge.

The committee also notes that there is little information concerning the immunogenicity or adverse event profile for AVA when administered to children, the elderly, or persons with chronic illnesses. Current knowledge of the vaccine's potential adverse health effects is derived from its use by a healthy adult population. While recognizing the challenges involved in conducting studies in vulnerable populations, the committee is persuaded that efforts to study the use of AVA in children, the elderly, and persons with chronic illnesses should be a high priority once the findings from the human clinical trial have established the optimal route (SQ versus IM) and number of AVA doses for young and middle-aged adults. The planning for future studies in vulnerable populations should be flexible enough to respond to changing circumstances, including the possible availability of a newer anthrax vaccine.

Recommendation: Studies of the use of AVA (and any future anthrax vaccine) by children, the elderly, or persons with chronic illnesses should have a high priority once the findings from the clinical trial have established the optimal route and number of vaccine doses in

young and middle-aged adults. The possible availability of newer-generation anthrax vaccines should be taken into account in planning these future studies in vulnerable populations.

Although the congressional mandate might seem to confine CDC to studies of pre-exposure use of the current anthrax vaccine, the committee urges CDC to interpret the congressional mandate broadly in order to improve preparedness for the possibility of future bioterrorist events involving anthrax. The research program must be flexible enough to respond to changing circumstances by using both intramural and extramural resources, and to draw fully upon the expertise in vaccine development and testing available within NIH and DoD.

A NEED FOR A SINGLE PROGRAM LEADER

From its review, the committee sees evidence of a need for strong internal overall leadership of the CDC anthrax vaccine research plan to provide management and oversight. Although the research plan responds well to the specific elements of the congressional mandate, it currently includes studies that the committee concluded should have a low priority or should not be conducted, and it omits studies that the committee considers important. In the absence of authoritative centralized senior leadership, individual projects within programs can sometimes gain a momentum of their own and become difficult to modify or stop, even if they are no longer appropriate.

Given the size of the task and the nature of the work, it is appropriate that the anthrax vaccine research program receive high-level attention and direction from the leadership at CDC. However, it does not appear that it has. Despite hard work from the two units involved in developing and improving the proposals and protocols for the individual studies that make up the research program, the research program still appears to lack a comprehensive plan to guide its continued overall development.

The committee found two groups of studies being planned and carried out by two separate organizational units within CDC but drawing on a single ongoing source of funds. The committee is persuaded that effective coordination of the anthrax vaccine research program requires management by a single senior CDC biomedical scientist who has responsibility for the overall program. In addition to setting priorities and guiding strategic planning for the research program, a clearly defined leader can facilitate appropriate responses to changing circumstances and new opportunities that may arise.

Recommendation: CDC should establish clearly defined senior leadership for the anthrax vaccine research program to articulate precise objectives for the research plan and to provide authority and accountability in the management of a coherent research plan. A single senior biomedical scientist should be given management authority for the entire program.

A research program of this size and visibility can also benefit from ongoing guidance from a group of external scientific advisors who can assist in planning and setting priorities. This IOM committee has provided input for planning and prioritizing studies in the research plan, but it cannot continue in this role and moreover is not well suited to providing ongoing real-time advice. Although CDC responded to the committee's prior recommendation to convene scientific advisory panels for individual studies, there is no indication that CDC will have a future source of external advice to the research program as a whole.

The overall program should be overseen by an external advisory committee that will provide scientific recommendations to the program leadership on terminating studies or redirecting program resources. Recognizing that the administrative and procedural requirements related to such groups can be burdensome and time-consuming, the committee encourages CDC to seek the most efficient means of gaining access to ongoing expert scientific guidance.

Recommendation: As soon as possible, CDC should convene an external advisory group for the overall anthrax vaccine research plan and its progress. This group should have an advisory role regarding the continuation or termination of studies that are under way, the initiation of new studies, and the direction of the entire program.

Boxes ES-2, ES-3, ES-4, and ES-5 provide a complete listing of the findings and recommendations from this report. Subsequent chapters provide background for these findings and recommendations.

BOX ES-2
CHAPTER 4 FINDINGS AND RECOMMENDATIONS

Finding: As described in the study protocol, the human clinical trial is generally responsive to the congressional mandate and to important research needs for determining immunologic correlates of protection, documenting the immunogenicity of AVA, and optimizing the vaccination schedule and routes of administration of AVA.

Finding: The HLA substudy experiments as described are not critical to resolving the concerns regarding the safety and efficacy of AVA. As part of the CDC anthrax vaccine safety and efficacy research program, the studies should be considered of low priority.

Recommendation: CDC should consult with FDA and receive their approval regarding the type of analysis (according to protocol, intent to treat, or other) that will provide appropriate support for a change in the labeling of AVA regarding the route of administration and the number of doses required.

Finding: The committee finds that the nonhuman primate studies that have been proposed as a means to provide information about the efficacy of AVA are well designed and responsive to the congressional mandate and to important research needs. The information gathered will inform and influence the development and licensure of new protective antigen-based anthrax vaccines.

Recommendation: Careful characterization of the vaccine lots used in the clinical trial and nonhuman primate studies is crucial. Protocols for this work should undergo review by the expert consultative panel convened for laboratory issues.

Recommendation: CDC should consult with the Statistics Panel for expert guidance on analyses of data from the nonhuman primate studies, including devising appropriate methods for handling missing data.

Finding: Passive protection studies are important for improving understanding of the mechanism(s) of the efficacy of AVA and can help to address practical issues related to the management of anthrax disease.

Recommendation: CDC should conduct passive protection studies as part of its anthrax vaccine safety and efficacy research program.

Finding: Research is needed to understand better the effect of the size of the challenge dose on the protection afforded by AVA.

Recommendation: CDC should support or conduct research on the effect of the size of the challenge dose on immunity provided by vaccination with AVA.

Finding: The committee strongly supports the use of validated assays that can be standardized across the field of anthrax vaccine research. CDC's development and validation of such assays will provide an important contribution in this regard.

Recommendation: CDC should give high priority to standardization of assays that can be used across laboratories conducting research with anthrax vaccine.

Finding: The biopsies of lymph nodes and bone marrow and the bronchoalveolar lavage planned as part of the Immune Correlates of Protection Study require multiple invasive procedures that do not appear to be adequately justified.

BOX ES-2 CONTINUED

Recommendation: On the basis of the information provided to the committee for evaluation, the committee recommends that the NHP studies requiring multiple samplings from biopsies of lymph nodes and bone marrow and from bronchoalveolar lavage should not be continued in their current form. If such studies can be adequately justified, they should be modified to require fewer invasive procedures.

Finding: With the exception of the biopsy and bronchoalveolar lavage studies noted above, the committee finds that the ICP studies that have been proposed as a means to provide information about the efficacy and immunogenicity of AVA are responsive to the congressional mandate and to important research needs. The information gathered will inform and influence the development and licensure of new PA-based anthrax vaccines.

BOX ES-3
CHAPTER 5 FINDINGS AND RECOMMENDATIONS

Finding: As described in the study protocol, the human clinical trial is generally responsive to the congressional mandate to evaluate the incidence of, risk factors for, and differences between men and women in local and systemic immediate-onset health effects associated with AVA and the effect of the route of vaccine administration on adverse events. The study will also provide a 42-month follow-up period during which to monitor the occurrence of later-onset health effects.

Recommendation: The analyses of reactogenicity in CDC's human clinical trial of AVA should use two-sided statistical tests.

Finding: The committee concludes that the preliminary exploration of a study of possible chronic or later-onset adverse events related to anthrax vaccination among goat-hair textile mill workers, with community and occupational comparison cohorts, was appropriate. That effort, however, has produced sufficient information to indicate that the study (1) poses the risk of generating spurious associations or masking real associations, in part because of the difficulty of identifying suitable comparison groups, and (2) would not have sufficient statistical power to detect conditions of interest. Furthermore, with these limitations, conducting the study poses the risk of generating unwarranted health concerns among the participants.

Recommendation: CDC should not continue work on the proposed follow-up study of textile mill workers who received AVA.

Finding: Postmarketing-type cohort studies of anthrax vaccine use are appropriate for two purposes:

1. to confirm in a population not participating in a clinical trial the findings from the clinical trial regarding rates of adverse events commonly associated with receipt of AVA, differences between subcutaneous and intramuscular administration in rates of adverse events, and risk factors for adverse events, and
2. to detect rare but medically significant adverse events that will be found only by observing a larger population over a longer period of time than is possible in the human clinical trial.

Recommendation: A VHC-based study to verify reaction rates to AVA and the validity of self-reported data observed in the clinical trial should provide for intensive active surveillance of relatively small cohorts, similar in size to the study groups for the human clinical trial.

Finding: Because of the anticipated labeling change that will specify intramuscular administration of AVA, a VHC-based study of adverse events must be initiated promptly if it is to follow a cohort of military personnel who receive AVA subcutaneously.

BOX ES-3 CONTINUED

Finding: A large cohort study intended to detect the occurrence of less common, medically significant adverse events following receipt of AVA would require the inclusion of a control group that has not received AVA and that is comparable in initial health status to the vaccinated cohorts. Because vaccination is related to deployment and deployment is related to health status, it would be challenging to assemble a suitable control group.

Finding: The SF-36 is designed to detect large changes in health status. It is not suitable for distinguishing differences in health-related quality of life among basically healthy people such as the military personnel who will receive AVA. Furthermore, in the proposed study population, the confounding effects of exposure to other vaccines and particularly of the experience of deployment are likely to make it difficult to discern any unique effect associated with the receipt of AVA.

Recommendation: CDC should not conduct the proposed VHC-based study of the effect of AVA vaccination on health-related quality of life.

Finding: The VHC-based study of the effect of women's hormonal phase on the occurrence of adverse events following receipt of AVA, would be addressing a complex subject with many potentially confounding factors (e.g., age, race, parity).

Recommendation: As currently described, the VHC-based study of the relationship between women's hormonal phase and the occurrence of adverse events following receipt of AVA should have a low priority in the CDC research program.

Recommendation: An external scientific advisory group should be constituted to provide guidance to CDC and DoD on all research undertaken through the VHC network. Given the draft study proposals reviewed by the committee, the advisory group should include, among others, experts in biostatistics (propensity analysis), health care outcomes assessment, pharmacoepidemiology (postmarketing surveillance), and clinical epidemiology (medically unexplained symptoms).

Finding: The application of data mining and other statistical analysis techniques to screen data from VAERS and from DMSS data sets is still experimental.

Recommendation: Hypothesis generation using data mining and other statistical techniques for screening data should be tested and validated in DMSS or other structured data sets before being considered for use with VAERS. Only if these techniques can be validated with a structured data set and then with VAERS data should they be used to generate hypotheses from VAERS concerning adverse events and AVA.

Finding: DMSS is a uniquely valuable resource for testing hypotheses regarding medically significant health effects, especially possible later-onset effects, of exposure to AVA or other vaccines, especially those that might arise several months after vaccination but within the period of active duty.

Recommendation: CDC should work with DoD to follow up the signals regarding AVA that have already been generated by the review of VAERS reports and preliminary analyses of DMSS data on hospitalization and outpatient visits (see IOM, 2002).

Recommendation: Analysis of DMSS data should be the primary approach for investigation of possible AVA-related health effects of medical significance that occur within the typical period of active duty following vaccination (perhaps as much as 3 to 4 years on average).

BOX ES-3 CONTINUED

Recommendation: To allow for analysis of health effects of AVA that might arise following the completion of active duty, CDC should investigate the use of DMSS data in conjunction with morbidity and mortality data from the Millennium Cohort Study and the health system of the Department of Veterans Affairs. Deaths of military personnel identified through DMSS could be tracked through resources such as the Beneficiary Identification and Records Locator Subsystem of the VA, the Social Security Administration, and the National Death Index.

Recommendation: Adequate resources (substantially more than can currently be identified from the CDC–DoD Memorandum of Understanding) should be made available to support the use of DMSS data for testing hypotheses regarding health effects related to AVA or other vaccine exposures.

Finding: An overall study plan or strategy is needed to guide CDC's use of VAERS, DMSS data sets, and other data sources for hypothesis-generating and hypothesis-testing activities related to AVA.

Recommendation: CDC, working with DoD, should establish a staff team with overall responsibility for the review and analysis of VAERS and DMSS data for both hypothesis generation and hypothesis testing related to AVA.

Recommendation: A committee of nongovernmental experts should be established to periodically advise CDC on plans and priorities for the analyses of data from DMSS and other sources to test hypotheses regarding health effects related to AVA.

Finding: Widespread environmental exposure to aluminum makes it difficult to conduct a study of potential adverse effects of exposure to the aluminum hydroxide adjuvant/adsorbant in AVA.

Finding: The significance of the presence of aluminum in tissue biopsies of persons diagnosed with the condition called macrophagic myofasciitis has not been established.

Recommendation: The study of the possible role of the aluminum hydroxide adjuvant in adverse events following receipt of AVA should be eliminated from the CDC research program.

BOX ES-4
CHAPTER 6 FINDINGS AND RECOMMENDATIONS

Finding: With its large sample size, the current design of the study of knowledge, attitude, and beliefs regarding AVA primarily addresses the acceptability of the vaccine among military personnel. Further documentation of the prevalence of attitudes and beliefs regarding the vaccine is unlikely to significantly advance the acceptability of the vaccine, which should be the major goal. Instead, qualitative research techniques such as focus groups and smaller-scale surveys can be used to determine the breadth, depth, and underlying reasons for the attitudes and beliefs regarding AVA. This information can serve as the basis for targeted interventions, the impact of which can be assessed with subsequent surveys.

Recommendation: In view of the study timeline and research needs, CDC should modify the design of the KAB study of military personnel to focus on more timely development of educational interventions and the evaluation of their impact on the acceptability of AVA and a broader range of vaccines, including a new anthrax vaccine.

Finding: Potential differences between racial and ethnic groups in knowledge, attitudes, and beliefs about AVA and military vaccines generally may be important.

Recommendation: CDC should design the focus groups and preliminary survey to take into account different racial and ethnic groups.

Finding: As proposed, the survey of civilian and military health care providers has a focus on knowledge, attitudes, and beliefs concerning VAERS and vaccination with AVA. Additional questions oriented toward the development of educational materials concerning AVA and other vaccines, immunization, and adverse events could broaden its usefulness. In addition, further articulation of links between the study and development of educational materials is needed.

Recommendation: In addition to gathering information on KABs about VAERS and the current anthrax vaccine, CDC should modify the survey of health care providers to study KABs about a new anthrax vaccine, other military vaccines, and vaccines in general, with a focus on information useful for timely development and testing of appropriate educational materials. The study population should include health care providers who may treat service members with adverse events following vaccination, as well as those who administer vaccines.

BOX ES-5
CHAPTER 7 FINDINGS AND RECOMMENDATIONS

Finding:

1. With respect to the tasks specifically outlined in the congressional mandate, CDC's research response is generally complete and appropriate.

2. When considered as a whole, however, the research program has elements that are of low priority and other elements that are inappropriate and should not be carried out as planned.

Finding: Additional studies in laboratory animals of the efficacy of AVA in combination with antibiotics following inhalational exposure to anthrax spores are needed to establish an appropriate duration for antibiotic prophylaxis after vaccine administration (see IOM, 2002).

Recommendation: As part of its research plan, CDC should support studies in laboratory animals to establish an appropriate duration for antibiotic prophylaxis when administered with AVA following *B. anthracis* spore challenge.

Finding: The exposure of members of the civilian population to anthrax spores in the bioterrorist incidents in the fall of 2001 demonstrates the importance of determining the immunogenicity and reactogenicity of AVA or any future anthrax vaccine when used by children, the elderly, and persons with chronic illnesses.

Recommendation: Studies of the use of AVA (and any future anthrax vaccine) by children, the elderly, or persons with chronic illnesses should have a high priority once the findings from the clinical trial have established the optimal route and number of vaccine doses in young and middle-aged adults. The possible availability of newer-generation anthrax vaccines should be taken into account in planning these future studies in vulnerable populations.

Finding: The CDC anthrax safety and efficacy research program lacks clearly defined senior leadership. It also lacks an ongoing external review committee that is independent of the consultative groups for individual studies.

Recommendation: CDC should establish clearly defined senior leadership for the anthrax vaccine research program to articulate precise objectives for the research plan and to provide authority and accountability in the management of a coherent research plan. A single senior biomedical scientist should be given management authority for the entire program.

Recommendation: As soon as possible, CDC should convene an external advisory group for the overall anthrax vaccine research plan and its progress. This group should have an advisory role regarding the continuation or termination of studies that are under way, the initiation of new studies, and the direction of the entire program.

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1

Introduction

Anthrax is a disease caused by *Bacillus anthracis*, a spore-forming bacterium whose characteristics of stability and availability make it a feasible choice for biological warfare. Examples of weapons development programs using *B. anthracis* are well known, but the distribution of anthrax spores through the United States postal system in the fall of 2001 considerably heightened awareness of the risks from anthrax and brought additional interest in the disease and its prevention through the use of the vaccine Anthrax Vaccine Adsorbed (AVA). This report is a review of plans by the Centers for Disease Control and Prevention (CDC) for a congressionally mandated research program on the safety and efficacy of the anthrax vaccine.

As described below, the motivation for the CDC anthrax vaccine safety and efficacy research program was concerns about the vaccine among some military personnel and members of the public following the start of mandatory immunizations against anthrax for the military in 1998. However, the bioterrorist events of 2001 radically altered perspectives on the need for anthrax vaccine, making what had been a hypothetical risk—exposure to aerosolized anthrax spores—seem far more concrete. The bioterrorist events have had widespread ramifications, including vigorous government efforts to accelerate the development and licensure of a new anthrax vaccine.

The committee's evaluation of the CDC anthrax safety and efficacy research program has necessarily been affected by this change in context. In particular, the timeline for the CDC research plan must be viewed in the context of plans for tremendously accelerated development of a new anthrax vaccine. While many of the planned studies would provide information that is relevant to the development and understanding of a new vaccine as well as the current one, some data about the safety and efficacy of the currently licensed vaccine could conceivably come too late to be useful. The committee acknowledges that the changed situation has put great demands upon CDC and hopes that this report will provide advice that will help optimize the usefulness of the research program.

The research program will also be affected by other circumstances beyond CDC's control, such as the timing and extent of the resumption by the Department of Defense (DoD) of its anthrax vaccination program for the military. Similarly, the timeline for the availability of a new licensed vaccine is uncertain. Bearing in mind these uncertainties, the committee strove to focus on addressing the research questions that stand regardless of these circumstances.

ORIGIN OF THE STUDY

Concerned that biological weapons using anthrax might be directed against the U.S. military, in December 1997 DoD announced a program to vaccinate all service personnel against anthrax using the li-

censed product AVA. The vaccination plan was to be phased in gradually, starting with service members judged most likely to encounter the threat. The first vaccinations under DoD's Anthrax Vaccine Immunization Program (AVIP) took place in March 1998. As more members of the military received the mandatory vaccine doses, some raised concerns about the safety and efficacy of the vaccine being administered.

Because of the importance of protecting service personnel from potential acts of biological warfare using *B. anthracis*, and because of concern among troops and their families about adverse events possibly associated with the anthrax vaccine, the U.S. Congress has also been interested in the anthrax vaccine and the DoD immunization policy. In its appropriations for the Department of Health and Human Services for fiscal year 2000, Congress provided funding for CDC to carry out a research program on vaccines used against biological agents. The request is found in Box 1-1 below.

As it began planning a research program to respond to this mandate, CDC sought the input of the Institute of Medicine (IOM) regarding its developing plan. CDC contracted with IOM to establish an expert panel to review the completeness and appropriateness of the CDC anthrax vaccine safety and efficacy research program. The committee's Statement of Task is found in Box 1-2.

BOX 1-1
Congressional Request for CDC Anthrax Vaccine Research, FY 2000–1

Public Law 106-113 provided fiscal year 2000 funding

"to the Centers for Disease Control and Prevention (CDC) for a collaborative effort to study the safety and efficacy of vaccines used against biological agents. The study would address: (1) the risk factors for adverse events, including differences in rates of adverse events between men and women; (2) determining immunological correlates of protection and documenting vaccine efficacy; and (3) optimizing the vaccination schedule and administration to assure efficacy while minimizing the number of doses required and the occurrence of adverse events. It is intended that NIH, CDC, and the Department of Defense will fully cooperate in this effort."

The excerpt of Public Law 106-113 above is the language that formed the basis of the contract for this project. In the succeeding year, Congress made additional comments as follows in the House–Senate conference report that was generated in conjunction with fiscal year 2001 appropriations legislation, with fiscal year 2001 funding provided by Public Law 106-554.

"Regarding the anthrax study, the conferees understand that clinical studies will be greatly facilitated by the establishment of the Vaccine Healthcare Center Network, with the first site at Walter Reed Army Medical Center. This Network will facilitate data collection, standardization of the anthrax immunization, training and general data collection for this project."

BOX 1-2
Committee to Review the CDC Anthrax Vaccine Safety and Efficacy Research Program
Statement of Task

This committee will advise the Centers for Disease Control and Prevention (CDC) on the completeness and appropriateness of the CDC plan to respond to the Congressional mandate to study the safety and efficacy of anthrax vaccine, addressing: (1) risk factors for adverse reactions, including gender differences; (2) determining immunologic correlates of protection and documenting vaccine efficacy; (3) optimizing the vaccination schedule and routes of administration to assure efficacy while minimizing the number of doses required and the occurrence of adverse events. The CDC, the National Institutes of Health (NIH), and the Department of Defense (DOD) are directed by Congress to collaborate and cooperate fully in this effort.

STUDY PROCESS AND INFORMATION SOURCES

The IOM convened the Committee to Review the CDC Anthrax Vaccine Safety and Efficacy Research Program in fall 2000. Reflecting elements in the charge to the committee, members brought expertise in microbiology; infectious diseases; vaccine research, development, and evaluation; postmarketing surveillance of adverse events; regulatory and licensing procedures; epidemiology; biostatistics; survey research and design; immunology; differences in disease between men and women; and health surveillance (see Appendix A for biographical sketches of the committee members). The charge to the committee did not include evaluation of the safety and efficacy of the current vaccine. This topic was the subject of a recent report of another IOM committee, the Committee to Assess the Safety and Efficacy of the Anthrax Vaccine (IOM, 2002). Four members of that committee also served on the Committee to Review the CDC Anthrax Vaccine Safety and Efficacy Research Program. The charge to the present committee was limited to a review of the research program and did not encompass review of other aspects of the CDC anthrax vaccine program, such as clinical or operational efforts related to administering the anthrax vaccine.

The committee based its evaluation of the CDC research plan primarily on information provided by CDC. At five open meetings, the committee heard presentations from CDC investigators about their developing research plans. CDC also provided written materials to the committee describing the research plans. To better understand the context in which the research was requested and planned, the committee also heard in one of its open meetings from service members and others with concerns about the safety or efficacy of the vaccine. The dates, locations, and agendas of the public workshops are provided in Appendix B. In addition to meetings held in conjunction with its public sessions, the committee met in two closed sessions and two telephone conferences to deliberate and to draft its report.

Because CDC research plans continued to evolve during the first year of the committee's work, the committee requested that CDC provide a document that described the complete research plan as of February 2002. The committee also requested other specific information, such as an integrated timeline and a comprehensive list of critical research questions in anthrax vaccine research. The document describing the research plan and the accompanying study protocols that CDC provided in response to the IOM request received significant emphasis in the committee's evaluation of the research plan, supplemented by information gathered and discussed in the committee meetings. A subset of these documents is provided in Appendix C.

The original timeline for the IOM review of the CDC research plan called for an interim report to be delivered by June 30, 2001, and a final report by the end of the original task order period (August 2002). The committee provided its interim report to CDC on June 25, 2001, and the report was publicly released in July 2001. Subsequently, the government's response to the bioterrorist events of fall 2001 placed tremendous demands on CDC's time and resources. Expertise that would otherwise have been applied to further development of the CDC anthrax safety and efficacy research plan was instead appropriately redirected in part toward response to the anthrax exposures and cases. CDC requested that IOM delay its activities for a period of several months, and the contract was extended to conclude on December 31, 2002.

INTERIM REPORT

The committee's interim report of July 2001 (IOM, 2001) provided its findings and recommendations as of that time, which was fairly early in CDC's planning and development of the research program. The committee found that the CDC had not yet developed—or not communicated—a comprehensive plan for the anthrax vaccine safety and efficacy research program. Nevertheless, the committee concluded that despite the absence of a comprehensive plan, the CDC program included appropriate and well-conceived scientific projects generally responsive to the congressional mandate. Many projects were still not fully developed and described at the time, however. The committee's major recommendations in the interim report were that CDC should produce a comprehensive description of its research program, with a statement of its goals and how the plans would meet the goals. The report also recommended that CDC should

consider engaging experts to provide immediate consultation on technical matters of study design and execution. Another recommendation was that CDC should continue and further strengthen the mandated collaboration with DoD and NIH, for example, by making more extensive use of DoD's Defense Medical Surveillance System (DMSS). A full listing of the findings and recommendations from the interim report appears in Appendix F. The report can be found on the Internet at http://www.nap.edu/catalog/10157.html.

RELATED REPORTS

Because of the controversy surrounding the military's mandatory vaccination program and heightened concerns regarding the use of anthrax as an agent of terrorism or warfare, two key reports have been released in recent years regarding the anthrax vaccine. While they are not directly related to the subject of this report on the CDC research plan, they provide context for the research needs discussed.

ACIP Recommendations

In December 2000, a report regarding recommendations for use of the anthrax vaccine was released by the Public Health Service's Advisory Committee on Immunization Practices (ACIP) (CDC, 2000). In *Use of Anthrax Vaccine in the United States*, ACIP reviewed safety and efficacy data and recommended routine vaccination with AVA for those working with large quantities or concentrations of *B. anthracis* and those conducting activities with a high potential for production of aerosolized *B. anthracis* (CDC, 2000). ACIP did not recommend pre-exposure vaccination for emergency first responders, federal responders, medical practitioners, or private citizens for bioterrorism preparedness because "the target population for bioterrorist release of *B. anthracis* cannot be predetermined, and the risk of exposure cannot be calculated . . . . For the military and other select populations or for groups for which a calculable risk can be assessed, pre-exposure vaccination may be indicated" (CDC, 2000, p. 12).

Since the release of that report, the intentional distribution of anthrax spores in letters in the fall of 2001 and the subsequent illnesses and deaths from anthrax have heightened interest in the use of AVA for a wider population. At the time of this writing, however, ACIP had not altered its recommendations regarding the populations for whom vaccination is indicated.

IOM Report on the Anthrax Vaccine

In March 2002, the IOM Committee to Assess the Safety and Efficacy of the Anthrax Vaccine released the report *The Anthrax Vaccine: Is It Safe? Does It Work?* From its review of both published and unpublished data, the committee concluded that AVA as licensed is an effective vaccine to protect humans against anthrax, including inhalational anthrax. Because the vaccine exerts its protection via antibodies to protective antigen, which is crucial to the action of *B. anthracis* toxins, the report states that AVA should be effective against anthrax toxicity from all known strains of the bacterium, as well as from any potential bioengineered strains. Regarding safety, the report describes the committee's review of numerous case reports and many epidemiologic studies. From these data, the committee concluded that AVA is reasonably safe. Within hours or days following vaccination, it is fairly common for recipients to experience some local events (e.g., redness, itching, swelling, or tenderness at the injection site), while a smaller number of vaccine recipients experience some systemic events (e.g., fever and malaise). But these immediate reactions, and the rates at which they occur, are comparable to those observed with other vaccines regularly administered to adults. The committee found no evidence that vaccine recipients face an increased risk of experiencing life-threatening or permanently disabling adverse events immediately after receiving AVA, when compared with the general population. Nor did it find any convincing evidence that vaccine recipients face an elevated risk of developing adverse health effects over the longer term, although data are limited.

Regarding the manufacture of AVA, the committee reviewed and evaluated the steps taken by BioPort to win FDA approval of its production process following the shutdown of its facilities for renovation.

It took BioPort several years to receive FDA approval, and during that time supplies of the vaccine ran low, necessitating suspension of the military's vaccination program. With the newly validated manufacturing process being used in a renovated facility, AVA will be produced under strict controls that are in accord with current FDA requirements. The report states that the newly produced vaccine is expected to have greater assurance of consistency than the vaccine produced at the time of its original licensure.

The committee emphasized the importance of continued and improved monitoring efforts to detect any adverse health effects caused by AVA and other vaccines. In addition, studies are needed to quantify and correlate protective levels of antibodies in animals with antibody levels in humans after full immunization. Direct tests of the efficacy of AVA are neither feasible nor ethical in humans. However, correlates of protection can be derived from studies that use animal models to test the efficacy of AVA, as well as new vaccines against anthrax. Both passive and active protection studies have important roles. The report stressed that production, testing, and licensure of a new vaccine requiring fewer doses and producing fewer local reactions is needed. The findings and recommendations of the report are presented in Appendix G. The full report can be found on the Internet at http://www.nap.edu/catalog/10310.html.

ORGANIZATION OF THE REPORT

CDC has organized its Anthrax Vaccine Safety and Efficacy Research Plan into components of efficacy, safety, and acceptability. Accordingly, this report follows that structure to some extent. Chapter 2 provides background material about the disease known as anthrax, the licensed anthrax vaccine, and the questions regarding the efficacy and safety of AVA that prompted the congressional request for the CDC research program. Chapter 3 summarizes CDC's plan for the anthrax vaccine research program. In Chapter 4, the CDC research regarding the efficacy of AVA is described and the committee's findings and recommendations regarding this aspect of the research plan are presented. Chapter 5 describes the CDC research that is to address the safety of the anthrax vaccine, followed by the committee's discussion and evaluation. Chapter 6 reviews the research planned by CDC to address the acceptability of AVA and the committee's findings and recommendations about this research. In Chapter 7, the committee discusses and evaluates the completeness and appropriateness of the research plan as a whole.

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2

Background

Anthrax is primarily a disease of animals, and historically, humans have generally contracted the disease through contact with infected animals or contaminated animal products. Depending on the site of anthrax infection, disease can occur in three forms: cutaneous, gastrointestinal, or inhalational anthrax. The disease had become extremely uncommon in any form in the United States until the intentional distribution of anthrax spores through the postal system in the fall of 2001. These bioterrorist events led to 11 cases of inhalational anthrax, 5 of which were fatal, and to 8 confirmed and 4 suspected cutaneous anthrax infections (CDC, 2001b, 2002). More than 30,000 people may have been exposed to anthrax spores (CDC, 2001a,b).

Anthrax vaccines for use in animals were first developed in 1881 (Turnbull, 1991). Work on vaccines suitable for human use gained urgency in the 1940s because of fears that anthrax would be used as a biological warfare agent. A human vaccine was developed in the 1950s by the Army Chemical Corps and produced by a pharmaceutical company under contract with the Army. The current vaccine, Anthrax Vaccine Adsorbed (AVA), which differed minimally from the original preparation, was licensed in 1970 and was recommended for use by workers with occupational risk of exposure to anthrax, such as textile mill workers, veterinarians, and laboratory scientists.

In 1990, concerns that Iraq had biological weapons containing anthrax spores motivated the U.S. military to administer AVA to 150,000 or more service members deployed for the Gulf War. The existence of an Iraqi biological weapons program was confirmed in the mid-1990s (Henderson, 1999; Zilinskas, 1997), and in 1997, the Department of Defense (DoD) announced a plan to vaccinate all U.S. service members with the licensed anthrax vaccine. DoD's Anthrax Vaccine Immunization Program (AVIP) began in March 1998 with personnel scheduled for deployment to higher-risk areas (e.g., South Korea and Southwest Asia). By 2001, however, a limited supply of AVA had significantly slowed plans to vaccinate all military personnel.

The limited supply of AVA was the result of an interruption in vaccine production. In 1998, Michigan Biological Products Institute (MBPI), the manufacturer of the anthrax vaccine, stopped production to renovate the vaccine manufacturing facility after receiving notification from the Food and Drug Administration (FDA) that corrective actions were needed to avoid revocation of the facility's license (Zoon, 1997). In late 1998 the facility was transferred to its current owner, BioPort. Several FDA inspections were necessary before the facility reached compliance with FDA's manufacturing regulations. FDA approved the license supplement for the renovations of the BioPort facilities and for an offsite contract filling operation and released new vaccine lots in late December 2001 and January 2002 (Maseillo, 2001, 2002).

After the deliberate distribution of anthrax spores in bioterrorist incidents in the fall of 2001, AVA was offered in combination with antibiotics as prophylactic treatment for as many as 10,000 of the civilians who may have been exposed. Fewer than 200 chose to take the vaccine, which was offered under the provisions of an Investigational New Drug application because the vaccine is not licensed for postexposure use and the vaccine lot used had not yet been released by FDA.

In late June 2002, DoD announced a partial resumption of the AVIP (Wolfowitz, 2002; see Appendix E). Military personnel to be vaccinated under the resumed program are those "assigned to or deployed for more than 15 days in higher threat areas whose performance is essential for certain mission critical capabilities," with vaccination to begin 45 days before deployment, if possible.

This chapter briefly summarizes the basic pathophysiology of anthrax and the history of anthrax vaccine development. It describes some unanswered questions concerning the efficacy and immunogenicity of AVA and reviews the newly approved rule that permits FDA to use data from animal tests as the basis for evaluating the efficacy of vaccines and other products against certain lethal agents. The chapter then outlines the concerns that have been expressed by some people about adverse health outcomes that might be associated with use of AVA. Also described are two important tools for surveillance for adverse events following vaccination with AVA: the Vaccine Adverse Event Reporting System (VAERS) and the Defense Medical Surveillance System (DMSS).

ANTHRAX DISEASE

Anthrax is caused by infection with the bacterium *Bacillus anthracis*, a gram-positive, nonmotile, spore-forming organism (Brachman and Friedlander, 1999; Dixon et al., 1999). It is primarily a disease of wild and domestic animals exposed to spores in the soil. The spore form of *B. anthracis* is very hardy—anthrax spores can lie dormant in soil for many years and are resistant to physical and chemical challenges such as heat, dryness, and disinfectants.

As noted, depending on the site of anthrax infection, disease can occur in three forms: cutaneous, gastrointestinal, or inhalational anthrax. Cutaneous anthrax is generally associated with handling infected animals or their products and is manifested as a lesion that forms a vesicle and finally an ulcer marked by a characteristic black eschar. Eating meat from infected animals can lead to an oropharyngeal lesion (cutaneous-like anthrax inside the mouth or larynx) or to gastrointestinal anthrax, which can cause severe abdominal pain, bloody diarrhea, and ascites. Inhalation of aerosolized spores of sufficiently small particle size can cause inhalational anthrax, characterized by severe respiratory distress, with dyspnea, cyanosis, diaphoresis, and strident cough (Brachman and Friedlander, 1999). Radiographic examination of the chest usually shows a characteristic widening of the mediastinum and pleural effusions. Shock may develop, and hemorrhagic meningitis may occur in about 50 percent of cases (Brachman and Friedlander, 1999). Even with aggressive treatment, this form of anthrax has been associated with a high fatality rate within a matter of days after the onset of symptoms, which can initially resemble a common upper respiratory infection. Inhalational anthrax is generally seen only in industrial settings where conditions permit aerosolization of a sufficiently large number of spores in an enclosed area (Brachman and Friedlander, 1999).

After spores enter the body through any route, they are ingested by macrophages in a process called phagocytosis. Once in the macrophages, the spores germinate into vegetative bacteria that can multiply and secrete toxins that produce local edema and necrosis. If bacteria are carried to regional lymph nodes, they multiply further and produce additional edema and necrosis and enter the bloodstream to produce a systemic infection (Brachman and Friedlander, 1999; Dixon et al. 1999)

The virulence of *B. anthracis* derives from a bacterial capsule and three toxin proteins. The production of the capsule and toxin proteins is encoded on two separate plasmids, and both plasmids are required for full virulence. Plasmid pXO2 contains the gene that encodes the synthesis of a polyglutamyl capsule that inhibits phagocytosis of the vegetative bacteria. Plasmid pXO1 encodes the synthesis of the three toxin proteins: protective antigen (PA), edema factor (EF), and lethal factor (LF). To produce active tox-

ins, PA must bind to cellular receptors and then bind to either EF, to form edema toxin, or LF, to form lethal toxin. In both cases, PA appears to mediate binding of the toxin to the target cell and its translation to the cell's interior. EF is an adenylate cyclase dependent on the eukaryotic protein calmodulin (Brossier and Mock, 2001). EF is responsible for the ability of edema toxin to increase levels of cyclic adenosine monophosphate inside the eukaryotic cell, which interferes with the cell's water balance and results in edema. Edema toxin may also impair neutrophil function (Alexeyev et al., 1994; Dixon et al., 1999; O'Brien et al., 1985). LF is a zinc metalloprotease that cleaves two mitogen-activated protein kinase kinases. The mechanism by which lethal toxin, through the action of LF, leads to death of the host remains unknown but may involve suppression of the inflammatory response (Erwin et al., 2001; Pellizzari et al., 1999.)

ANTHRAX VACCINE

Attenuated spore vaccines against anthrax have been developed with bacterial strains missing one or both plasmids. The livestock vaccine currently in use in the United States and other countries, known as the Sterne vaccine, is derived from a noncapsulated *B. anthracis* variant that lacks the pXO2 plasmid. To develop an anthrax vaccine for humans, however, U.S. researchers used *B. anthracis* cultures in a synthetic medium without proteins or other macromolecules (Turnbull, 2000).

A production system for an anthrax vaccine for human use, first described in 1954 (Wright et al., 1954b), incorporated a chemically defined growth medium and a method of concentrating, stabilizing, and partially purifying PA by precipitation. A controlled trial to evaluate the safety and efficacy of this vaccine was conducted between 1955 and 1959 at goat hair-processing mills in the eastern United States (Brachman et al., 1962). The study indicated that the vaccine was effective in this population. The initial production method was soon modified for scale-up, with changes in the culture conditions, in the product purification method (a change from precipitation with alum to adsorption onto aluminum hydroxide gel), in the preservative (from thimerosal to benzethonium chloride, with formaldehyde as a stabilizer), and in the strain of the organism used, resulting in development of the currently licensed vaccine, AVA (Auerbach and Wright, 1955; Puziss and Wright, 1963; Wright and Puziss, 1957; Wright et al., 1962; see IOM, 2002 for a review of the changes). AVA is a cell-free filtrate containing PA as the principal immunogen. The anthrax vaccine is adsorbed to aluminum hydroxide (Alhydrogel), which acts as an adjuvant.[1]

AVA was licensed in 1970 for manufacture by the Michigan Department of Public Health. Michigan transferred its production plant to MBPI in 1995. In 1998, both the plant and the product line of MBPI were sold to BioPort, a private company that at the time of this report was the sole U.S. manufacturer of an anthrax vaccine for human use. The product license for AVA calls for subcutaneous administration of a basic series of six doses of 0.5 milliliters (ml) each. After administration of the initial dose, subsequent doses are administered at 2 weeks, 4 weeks, 6 months, 12 months, and 18 months. Annual booster doses are required.

The evidence to justify this dosing schedule is limited. Wright and colleagues (1954a) administered an alum-precipitated predecessor of AVA to 55 volunteers in two 0.5 ml injections given subcutaneously 2 weeks apart. A group of 660 people were then given 3 subcutaneous injections of the same vaccine at 2-week intervals, followed by a booster dose of 0.25 ml after 6 months. Brachman and colleagues (1962) used the same vaccine with a schedule of three 0.5 ml subcutaneous injections given at 2-week intervals, followed by three 0.5 ml booster doses given at 6-month intervals. Thereafter booster doses were given at yearly intervals. This schedule was then used for the studies leading to licensure of AVA. A pilot study has been conducted to evaluate changes in both the route of administration and the dosing schedule (Pittman et al., 2002). As described in detail elsewhere in this report, the Centers for Disease Control and Pre-

[1] An adjuvant is a component that augments the immune response. Many vaccines require adjuvants for efficient elicitation of an immune response.

vention (CDC) research plan includes a clinical trial to further evaluate the effect of these modifications on the safety and efficacy of the vaccine.

IMMUNOGENICITY AND EFFICACY ISSUES

Despite a body of evidence demonstrating the efficacy of AVA for prevention of anthrax disease in laboratory animals (reviewed in another report from the Institute of Medicine [IOM, 2002]), some important questions remain relating to the efficacy and immunogenicity of this vaccine. One need is to establish correlates of immunity to anthrax disease so that it will be possible to predict with a good degree of certainty whether an individual is sufficiently protected. While immunity to anthrax is associated with the presence of antibodies against PA, a quantitative relationship between protection and any correlate of immunity has not been firmly established (see IOM, 2002). Establishing an immune correlate of protection in animals will help to enhance understanding of the degree to which AVA or newly developed anthrax vaccines will be protective in humans. Both active protection studies and passive protection studies have crucial roles. The IOM study noted that passive protection studies involving the transfer of animal and human sera are "urgently needed to quantify the protective levels of antibody in vivo against different challenge doses of anthrax spores" (IOM, 2002, p. 75). Such studies can identify or confirm the amount of antibody to PA that must be present to provide protection against challenge by *B. anthracis* spores.

A related question that has arisen in light of the bioterrorist use of anthrax concerns the efficacy of AVA in contributing to protection from anthrax disease when the vaccine is administered in conjunction with antibiotics following exposure to anthrax spores (IOM, 2002). How long does it take to develop protective immunity, and therefore for how long must antibiotics be administered for postexposure protection? Clearly, antibiotics must be taken until the immune response reaches a protective level, and passive protection studies are needed to establish what that protective level is.

The IOM report also noted the need to standardize an assay for quantitation of antibody levels that can be used across laboratories carrying out research on anthrax vaccines (IOM, 2002). Such efforts are being undertaken as part of the CDC research program.

REGULATORY CONSIDERATIONS

The pilot study carried out by Pittman and colleagues (2002) evaluated the immunogenicity and adverse event profile associated with a change from SQ to IM administration of AVA and with the use of fewer doses of AVA. The study indicated that the IM route of administration was associated with fewer injection-site reactions and was as immunogenic as SQ administration, as indicated by anti-PA IgG antibodies and toxin neutralization antibody (TNA) assay. The data were also supportive of a reduction in the number of doses. Additional data confirming these findings are necessary to gain FDA approval to change the product license and labeling.

A human clinical trial to evaluate changes in the number of doses and the route of administration of AVA has been planned as part of the CDC research program. (The study is discussed in detail in Chapters 4 and 5.) CDC consulted with FDA to determine the criteria for establishing "non-inferiority" for immunogenicity, as well as the necessary measures for evaluating adverse events. If the data support a reduction in the number of doses required and/or a change in route of administration from SQ to IM, the vaccine will be easier to administer and more useful for the populations at high risk, at whom it would be targeted.

Although an improvement in the mode of administration of the currently licensed vaccine is needed, it is also crucial to move rapidly to a newer vaccine. However, a challenge faced with any vaccine developed to counter a potentially lethal agent such as anthrax or other biowarfare agents is the impossibility of directly evaluating its efficacy in humans. It would be neither feasible nor ethical to use humans to test the efficacy of anthrax vaccines against inhalational challenge, because there are no naturally occurring situations where humans are predictably at risk from airborne anthrax and the disease untreated is usually lethal.

In May 2002, FDA published a rule to address such situations (see Appendix D). The new rule amends the regulations governing new drugs and biological products to allow for the use in certain cases of appropriate studies in animals to provide evidence of the efficacy of products to reduce or prevent the toxicity of chemical, biological, radiological, or nuclear substances, when traditional efficacy studies in humans are not feasible and cannot be ethically conducted. Key provisions of the rule are stated as follows:

> . . . FDA can rely on the evidence from animal studies to provide substantial evidence of the effectiveness of these products when: 1) There is a reasonably well understood pathophysiological mechanism for the toxicity of the chemical, biological, radiological, or nuclear substance and its amelioration or prevention by the product; 2) the effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model (meaning the model has been adequately evaluated for its responsiveness) for predicting the response in humans; 3) the animal study endpoint is clearly related to the desired benefit in humans, which is generally the enhancement of survival or prevention of major morbidity; and 4) the data or information on the pharmacokinetics and pharmacodynamics of the product or other relevant data or information in animals and humans is sufficiently well understood to allow selection of an effective dose in humans, and it is therefore reasonable to expect the effectiveness of the product in animals to be a reliable indicator of its efficacy in humans. (FDA, 2002, p. 37989)

The rule, which became effective July 1, 2002, provides an outline to permit efforts to license new prophylactic measures for lethal agents, including new anthrax vaccines. CDC's planned nonhuman primate and correlates of protection studies, in conjunction with the human clinical trial, should indicate the levels of anti-PA antibodies or other immune response factors that correlate with protection from inhalational challenge. This information should be useful in the evaluation of a licensure application for a new anthrax vaccine that has been shown to be protective in animals and to stimulate an immune response that is expected to be protective in humans.

SAFETY CONCERNS ABOUT THE ANTHRAX VACCINE

An FDA review completed in 1975 classified AVA as safe and effective and found that use of AVA is indicated "only for certain occupational groups with a risk of uncontrollable or unavoidable exposure to the organism. It is recommended for individuals in industrial settings who come in contact with imported animal hides, furs, wool hair (especially goat hair, bristles, and bone meal), as well as in laboratory workers involved in ongoing studies on the organism" (FDA, 1985, p. 51058).

More widespread use of the vaccine during the Gulf War and as part of AVIP, however, resulted in new concerns about its possible association with serious acute and chronic health problems. Some proposed that vaccination with AVA could have contributed to the chronic multisystem health complaints of some Gulf War veterans (GAO, 1999a,b; Nicolson et al., 2000). With the expansion of mandatory vaccination under AVIP, there have also been concerns that the health impact of vaccination with AVA was being missed because adverse events were underreported to military health care providers and to VAERS (GAO, 1999c; Rovet, 1999). Reportedly, more than 400 members of the military who refused to accept vaccination with AVA have left military service voluntarily or involuntarily (Weiss, 2001). Mandatory vaccination against anthrax is also reported to have been an important factor to some Air National Guard and Air Force Reserve personnel when making their decision to leave military service or move to inactive status (GAO, 2000).

The symptoms associated with vaccination against anthrax that were reported by witnesses at congressional hearings and directly to this IOM committee included fever, headache and malaise, swelling, joint pain, and tinnitus (Bates, 2001; Moore, 2001; Starkweather, 2001; Vick, 2001). Several witnesses also reported conditions that they ascribed to receipt of AVA, including hypogonadism; Stevens-Johnson syndrome, which affected their vision as well as their skin; and a case of fatal aplastic anemia (Eberhart, 2001; Nietupski, 2001; Rugo, 2001).

As noted in Chapter 1, the IOM's Committee to Assess the Safety and Efficacy of the Anthrax Vaccine reviewed case reports and epidemiologic studies, both unpublished and published, and concluded from these data that AVA is reasonably safe, even though injection-site reactions such as redness, itching, swelling, and tenderness are fairly common (IOM, 2002). The committee did not find evidence that vaccinees face an increased risk of life-threatening or permanently disabling adverse events compared with non-vaccinees. The limited evidence did not indicate elevated risk for developing adverse events over the long term.

The IOM report identified some questions and needs still outstanding with respect to safety (IOM, 2002). Review of these needs and opportunities provides a context for evaluating CDC's plans for anthrax vaccine research. For example, the report recommended that individuals receiving vaccine from postrenovation lots of AVA should be monitored for possible health events. The capacity for effective use of DoD's DMSS to regularly test hypotheses that emerge from VAERS and other sources is needed. The report also stated that options for longer-term follow-up of the possible health effects of vaccination against anthrax should be evaluated, including collaboration between DoD and the Department of Veterans Affairs, and use of data from the Millennium Cohort Study.[2] A complete listing of the findings and recommendations of the IOM report is found in Appendix G.

VACCINE ADVERSE EVENT REPORTING SYSTEM

VAERS is a passive surveillance system begun in 1990 as part of the response to the National Childhood Vaccine Injury Act of 1986.[3] It is the nation's principal system for the collection of reports on adverse events following the use of any vaccine licensed in the United States. The system is co-administered by CDC and FDA.

Reporting to VAERS

VAERS receives spontaneous reports of adverse events following vaccination. Anyone can submit a report to VAERS, including vaccine recipients or their family members, and more than one report can be submitted about the same adverse event. Reporting is encouraged for any clinically significant event following vaccination and required for certain specified events (VAERS, 2001). Most reports are submitted by health care providers directly (30 percent) or through the vaccine manufacturer (42 percent) (Iskander, 2001b).

Each year, reporting forms along with instructions and a cover letter encouraging reporting are mailed to about 200,000 health care providers (Iskander, 2001a). The forms are also available on the Internet (http://www.vaers.org/, http://www.fda.gov/cber/vaers/vaers.htm, http://www.cdc.gov/nip/). A VAERS report form includes spaces for the reporter to provide demographic information about the vaccine recipient and an open-ended description of the adverse event(s), treatment, outcome, relevant laboratory or diagnostic information, timing of the vaccination and the adverse event, vaccine type and lot number, and preexisting conditions. Reports can be submitted by mail or fax, or the information can be provided over the telephone.

Limitations of VAERS

As the only system for the collection of information on adverse events reported in association with the use of all U.S. licensed vaccines after they are marketed, VAERS is an essential resource for the monitoring of vaccine safety. An unexpected increase in the numbers of reports about a product or a series of reports of an unexpected or unusual adverse event can catalyze additional information gathering

[2] The Millennium Cohort Study is a survey recommended by the U.S. Congress and sponsored by DoD. The study will monitor a total of 140,000 U.S. military personnel during and after their military service for up to 21 years to evaluate the health risks of military deployment, military occupations, and general military service (see http://www.millenniumcohort.org/about.html).

[3] National Childhood Vaccine Injury Act of 1986. P. L. No. 99-660 (1986).

and investigation. However, VAERS also has certain critical limitations (Chen, 2000; Ellenberg and Chen, 1997; IOM, 1994a,b). Adverse events that occur soon after a vaccination may be reported to VAERS whether or not they are causally related to the vaccination.[4] Duplicate reports of the same case may be submitted. The medical information provided on the form may be incorrect or incomplete. The complexity of the information that comes into the system (e.g., multiple exposures and multiple outcomes) also makes analysis difficult. In addition, VAERS provides no information on the incidence of similar events among persons who have not been vaccinated.

Because VAERS is a passive system that relies on spontaneous reporting, adverse events are likely to be underreported to an unknown extent, and underreporting may also vary over time and among various kinds of adverse events. One analysis found that the "reporting efficiency" of VAERS ranged from 68 percent for vaccine-associated poliomyelitis following administration of oral polio vaccine to less than 1 percent for rash following administration of the measles-mumps-rubella vaccine (Rosenthal and Chen, 1995). Moreover, for most vaccines there are no data about the number of doses actually administered, although there may be data from other sources on the number of doses distributed. As a result of these limitations, it is nearly impossible to calculate accurate rates of adverse events from VAERS data. A numerator based on the number of reports can be assumed to differ from the true number of events, and there are no data on the total number of doses administered for the denominator (Mootrey, 2000; Singleton et al., 1999; Tilson, 1992).

In the case of AVA, however, DoD has maintained records on vaccine doses administered since the start of the AVIP in 1998. This information provides a denominator that is useful in the interpretation of changes in the frequencies of conditions reported to VAERS. In addition, the availability of data from DMSS on diagnoses for hospitalizations and outpatient visits (see below) gives DoD a unique opportunity to evaluate the completeness of reporting to VAERS. Adverse events for which medical attention was received can be systematically identified within DMSS, and efforts can be made to determine whether those events are included in VAERS.

A spontaneous reporting system like VAERS should be used to generate signals of possible problems that can then be followed up by more specific investigations. The prior IOM report on AVA emphasized that increased reporting to VAERS is not a goal in and of itself (IOM, 2002). There is little expectation of complete reporting with spontaneous reporting systems like VAERS, and this inherent characteristic must be recognized to properly interpret the data that they produce. Instead, the IOM report encouraged more detailed and insightful reporting to VAERS (and other spontaneous reporting systems), including more clinical data on each case and the selective reporting of cases that are novel or serious, or both (IOM, 2002). The report also stated that more effort was needed in formal studies to follow up on the hypotheses emerging from VAERS.

DEFENSE MEDICAL SURVEILLANCE SYSTEM

Surveillance and analysis of adverse events following vaccination of military personnel are aided by the availability of databases that permit linkage of personnel and demographic information with information on military experience, location, immunizations, and medical events for active-duty personnel. The individual branches of the armed services maintain such databases, but even more useful are various DoD-wide databases, particularly the system of databases of health-related information (reported by each of the armed services) that make up DMSS (see http://amsa.army.mil/AMSA/AMSA_DMSS.htm). DMSS is coordinated by the Army Medical Surveillance Activity (AMSA).

[4] In response to a request from the Army Surgeon General, the Department of Health and Human Services convened a committee of civilian physicians and experts—the Anthrax Vaccine Expert Committee—who provide independent expert medical review of VAERS reports related to anthrax vaccination and attempt to assess the probability of a causal relationship between the reported adverse event and the anthrax vaccine. Further discussion of this committee and efforts to evaluate the likelihood of causal relationships between events reported to VAERS and any given vaccine can be found in IOM, 2002.

Medical data in DMSS are derived from Standard Inpatient Data Records and the Standard Ambulatory Data Records for all inpatient and outpatient encounters at military facilities. For each hospitalization, up to eight discharge diagnoses are coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Records on inpatient care in military medical facilities date from 1990 and those for ambulatory care begin in 1996. At present, the DMSS records on immunizations with AVA are more complete than those for immunizations with other vaccines. Records on reportable health events cover a set of diseases and health conditions named in the list of Tri-Service Reportable Events (AMSA, 1998; Mazzuchi, 1998). This list includes any adverse event following vaccination that results in admission to a health care facility or the loss from duty of more than 1 day.

Because DMSS and other DoD-wide databases can produce data on the entire population of active-duty military personnel and on the subpopulation vaccinated under AVIP, they have denominator data that are unavailable from VAERS, making it possible to assess vaccine-associated adverse event rates (number of adverse events/number of vaccine administrations) for some types of health events following vaccination. Adverse event rates can be compared between populations that did and that did not receive the vaccine. The DMSS databases also make it possible to monitor postvaccination medical histories over the length of active service. Even though this period is limited (typical Army enlistment is 2 to 6 years [Grabenstein, 2001]), it is a longer period of observation than that available for most vaccine safety studies.

Although DMSS is a substantially richer analytic resource than VAERS, it still has certain limitations. Whereas VAERS has the potential to receive reports on any type of adverse event following vaccination, including mild events, DMSS will capture only events that require inpatient or ambulatory medical care in a military facility or that result in the loss of time from duty. DMSS data may also be affected by problems common to large databases, such as administrative and operational differences in the ways data are collected and delays in the transmission of data from the systems in which they are originally collected. Ultimately, properly conducted studies performed using DMSS will often require access to primary medical records in order to validate medical diagnoses and obtain data that are not already in DMSS.

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3

The CDC Anthrax Vaccine Research Plan

In appropriations legislation for fiscal year 2000, Congress requested that the Centers for Disease Control and Prevention (CDC) implement a collaborative effort to study the safety and efficacy of the anthrax vaccine (AVA). The aim of this research was to (1) examine the risk factors for adverse events, including differences in rates of adverse events between men and women; (2) determine the immunologic correlates of protection and document vaccine efficacy; and (3) optimize the vaccination schedule and administration to assure efficacy while minimizing the number of doses required and the occurrence of adverse events. Congress also specified that CDC, the National Institutes of Health, and the Department of Defense (DoD) would fully cooperate in this effort.

The research program proposed and begun by CDC to respond to the mandate from Congress consists of an array of studies. These studies were described to the committee in written materials and oral presentations over the course of five committee meetings. Changes over time in these presentations and materials reflected the evolution of the plans for and implementation of the research program. Understanding that the research program would continue to develop, the committee requested a definitive description of the plan as of February 2002 to serve as a basis for its evaluation. CDC responded by providing the document "Anthrax Vaccine Safety and Efficacy Plan," dated February 22, 2002, which described or listed 11 studies (CDC, 2002c). This document is reproduced in Appendix C and is referred to in this chapter as the CDC Plan. It was accompanied by protocols or draft protocols for seven of the studies and less detailed descriptions of plans for the other four studies. These materials are the primary source of information used by the committee to evaluate the research program, supplemented by information gathered and discussed in the committee meetings. The committee's report and evaluation do not reflect changes that CDC has made in the program since February 2002.

The CDC Plan states that the studies and activities it describes are intended "to evaluate vaccine immunogenicity and correlates of protection; assess alternate vaccination schedules and routes of administration to enhance vaccine safety; and enhance reporting of adverse events after vaccination. In addition to evaluating the efficacy and short- and long-term safety of AVA, CDC and its partners will use a variety of approaches to improve the acceptance of AVA amongst military personnel"(CDC, 2002c, p. 3). The document notes that the implementation of the research plan will also provide scientific benefits for researchers in several disciplines and in development and validation of a new generation of technologically advanced vaccines.

The document provided to the committee by CDC listed objectives for three research categories: efficacy, safety, and acceptability. In response to a request from the committee, CDC also listed the critical research questions in these areas, with an indication of which of the proposed studies was designed to address each question and whether other organizations were addressing the question. This information, as

well as the prioritization CDC assigned to each study, is presented in three matrices (Tables 3-1, 3-2, 3-3). This chapter summarizes the studies that CDC has planned to address each set of research objectives. More detailed descriptions of the studies and the committee's review of each study are provided in Chapters 4, 5, and 6 of this report. The committee's overall assessment of the research plan is presented in Chapter 7.

The research studies are being carried out or managed at CDC by two units—the National Immunization Program (NIP) and the National Center for Infectious Diseases (NCID). As its name suggests, NIP is a disease-prevention program providing for the planning, coordination, and conduct of immunization activities nationwide (CDC, 2001). Its activities include providing consultation and training to assist health departments in planning, developing, and implementing immunization programs; administering research and operational programs for prevention and control of vaccine-preventable diseases; and supporting a nationwide framework for surveillance of vaccine-preventable diseases. NIP's support to health departments includes assistance in developing information management systems to monitor the safety and efficacy of vaccines by linking vaccine administration information with adverse event reporting and disease outbreak patterns (CDC, 2001). In keeping with these activities, the aspects of the anthrax safety and efficacy research program developed and overseen by NIP include studies of vaccine acceptability as well as of the use of data from the Vaccine Adverse Event Reporting System (VAERS) and the Defense Medical Surveillance System (DMSS) to improve information about adverse events following vaccination.

NCID is focused on the prevention of disease, disability, and death caused by infectious diseases and seeks to accomplish this goal by working with public health officials, health care professionals, and international groups (CDC, 2002a). The center's staff conducts surveillance, epidemic investigations, epidemiologic and laboratory research, training, and public education programs to develop and promote prevention and control strategies for infectious diseases. For the anthrax vaccine research program, NCID has developed and is managing three interrelated studies of the safety and efficacy or immunogenicity of the vaccine in both humans and nonhuman primates (NHPs).

The following sections review the research objectives and critical research questions described in the CDC materials.

EFFICACY

CDC's stated objectives for the efficacy component of its anthrax vaccine research program are displayed in Box 3-1.

The studies that have been planned to address efficacy and immunogenicity are (1) the Human Reactogenicity and Immunogenicity Trial (the Human Clinical Trial); (2) the Nonhuman Primate Vaccine Dose Ranging, Immunogenicity, and Challenge Trial (the NHP study); and (3) the Correlates of Protection Study (the ICP study). These studies are being carried out at or through NCID.

BOX 3-1
CDC Objectives for Research on the Efficacy of the Anthrax Vaccine

A. Assess AVA efficacy in humans immunized with AVA by measuring immune responses identified as protective in efficacy objective B (animal studies). Immune markers of protection will be evaluated by varying the number of priming shots and the route of administration.

B. Assess AVA efficacy in animals immunized with serial dilutions of AVA and challenged with live, inhaled anthrax spores.

C. Use blood samples from the subjects in the clinical trial and in animal studies to identify immune correlates of protection and validate laboratory studies to measure them.

SOURCE: CDC, 2002c, p. 10.

The Human Clinical Trial

The Human Clinical Trial is intended to compare the immunogenicity and reactogenicity of AVA when given under the currently licensed regimen (6 doses given subcutaneously over 18 months) with the immunogenicity and reactogenicity of the vaccine when given intramuscularly and with a reduced number of doses. It is anticipated to provide "the principal scientific basis for decisions regarding changes in route of vaccine administration and reduction in number of doses in the vaccination series" as well as "new understanding about anthrax pathogenesis and immunologic correlates of protection against inhalational anthrax in humans" (CDC, 2002c, p. 6). The work should also provide a scientific foundation for the development and licensing of the next generation of protective antigen (PA)-based anthrax vaccines.

The study is designed as a prospective, randomized, double-blind, placebo-controlled clinical trial to be conducted over a period of 43 months at five sites in the United States. The study population will consist of 1,560 healthy civilian adult men and women between the ages of 18 and 61 years. The study will be open to anyone meeting the eligibility criteria, but recruitment efforts will focus on groups for whom AVA vaccination for bioterrorism preparedness has been considered, including emergency first responders, federal responders, and medical practitioners. The analysis will compare men and women in terms of the reactogenicity of the vaccine and the influence of various risk factors on the occurrence of adverse events.

The study protocol received approval from the Food and Drug Administration (FDA) in fall 2001 and began enrolling participants in May 2002. CDC anticipates providing an interim analysis of the first 7 months of data to FDA in fall 2003, and presenting the final analysis to FDA in early 2007.

The Nonhuman Primate Dose-Ranging, Immunogencity, and Challenge Trial

The Nonhuman Primate Dose-Ranging, Immunogenicity, and Challenge Trial is planned to provide information from experiments with rhesus macaques about the relationship between immune responses developed from vaccination with AVA and protection from aerosol challenge with anthrax spores. Based upon the assumption that similar immune responses in humans and in nonhuman primates will be similarly protective, the study will help to provide information about the protection afforded by the vaccine (and other potential anthrax vaccines) in humans. The data will be used as evidence to support the objective of dose reduction and change in route of administration in the licensed AVA schedule for humans (CDC, 2002c). In addition, data on immune response will be collected and used in a related study (described next) to establish correlates of protection induced by AVA vaccination.

Rhesus macaques receiving a three-dose series of AVA at full dose or fixed dilutions of the full dose will be challenged with anthrax spores at different periods of time after vaccination. Vaccination with different dilutions of AVA is expected to induce different levels of immune response in the macaques. Rates of survival after lethal challenge of these animals will provide data to describe a relationship between immune response and survival. Blood sampling at intervals following vaccination and challenge will allow analysis of immune factors that may play a role in protection from challenge.

This study will be carried out at two sites. It began with vaccination of some of the animals in early 2001. Plans call for completion of the study in 2004, but data available before then could be used by FDA in making a decision concerning the potential application for a label change to permit the use of fewer doses or a different route of administration in humans.

Studies of Immune Correlates of Protection (ICP) Against Inhalational Anthrax

Studies of Immune Correlates of Protection (ICP) Against Inhalational Anthrax are planned to identify components of the rhesus macaque humoral and cell-mediated immune responses to AVA that correlate with protection against aerosol challenge by virulent *B. anthracis* (CDC, 2002f). The ICP studies will develop and apply a panel of immunologic assays to carry out this work.

The emphasis in the ICP studies is on the description and quantification of antibody responses to PA, lethal factor, and edema factor, using quantitative anti-PA IgG enzyme-linked immunosorbent assay and toxin neutralizing antibody assay. The same assays are being used in the human clinical trial as primary endpoints for evaluating the immunogenicity of alternative dosing schedules and routes of vaccine administration. The studies will also include more detailed analyses of the humoral response, as well as analysis of cellular immune response factors.

The studies, which are being carried out at three different sites, began in March 2001, with the first vaccinations of about half of the animals. They will follow the timeline of the closely related human clinical trial and NHP studies, with a preliminary analysis to be presented to FDA in the first quarter of 2004, and the final analysis scheduled for presentation to FDA in the first quarter of 2007.

SAFETY

CDC's stated objectives for the safety component of its anthrax vaccine research program are displayed in Box 3-2.

The studies that address the subject of adverse events are (1) the human clinical trial, (2) a study to look for long-term adverse events, (3) cohort studies conducted in collaboration with the Vaccine Healthcare Centers (VHC) Network, (4) analysis of data from VAERS and DMSS, and (5) investigation of the possible role of the aluminum hydroxide adjuvant in adverse events following AVA vaccination.

Anthrax Vaccine Adsorbed: Human Reactogenicity and Immunogenicity Trial to Address Change in Route of Administration and Dose Reduction

The human clinical trial, described above in connection with the efficacy studies, will also provide data regarding adverse events following vaccination with AVA. CDC has proposed two study hypotheses related to reactogenicity and adverse events:

1. AVA administered by the IM route results in local reactogenicity that is decreased compared to that of SQ administration.
2. Occurrence of adverse events following AVA administration is influenced by selected risk factors. (CDC, 2002b,e)

The human clinical trial is therefore planned to provide information to permit a comparison of the rates of adverse events observed following AVA vaccination via the IM route with those observed with vaccination via the SQ route. The study will also be able to gather data on the risk factors for adverse events. Information about the study design and timeline was presented briefly above, and more detail regarding the safety aspects of the study is provided in Chapter 5.

Follow-up Study of Textile Mill Workers Vaccinated Against Anthrax

CDC has planned a retrospective cohort study to assess the possibility of chronic or later-onset adverse health effects associated with AVA vaccination. The study plans call for an examination of the mortality experience and functional status of textile mill workers who received doses of AVA 10 or more years ago. The study population is to be drawn from former workers at a textile mill that processed goat hair from the mid-1960s through the mid-1990s. CDC proposes to identify these workers through Social Security records and then to either locate survivors or obtain death certificates for those no longer alive. This process is expected to produce a study population of about 1,500 persons, based on assumptions that 15 percent of survivors will be lost to follow-up and that 70 percent of those located will participate.

Two comparison groups of unvaccinated persons are planned: one group drawn from the community in which the goat hair mill was located, and a second comparison group of persons who worked in other kinds of textile processing mills in the same region and time period as the members of the vaccinated study group.

BOX 3-2
CDC Objectives for Research on the Safety of the Anthrax Vaccine

- To investigate potential long-term sequelae of AVA.
- To gain a better understanding about the type, frequency, and gender differences of vaccine adverse events associated with AVA.
- To evaluate the completeness and accuracy of reporting of AVA adverse events in the military and to develop and implement interventions to improve AVA adverse events reporting and surveillance.
- To assess AVA administration practices and the military immunization health care system that may impact AVA adverse events, and to enhance AVA delivery practices (quality assurance of AVA administration services in the military).
- To evaluate concerns that military personnel may have about AVA and improve their knowledge and understanding about the risk benefit of AVA and other vaccines.
- To provide AVA information, education, and communication resources to the civilian public and to military personnel in collaboration with the Department of Defense.

SOURCE: CDC, 2002c, p. 11.

Information is to be collected about participants' demographic and socioeconomic characteristics and about health-related risk factors. Death certificates will be obtained to determine the date and cause of death for vaccinated workers who have died. Among survivors, if data from the self-reported medical histories reveal a statistically significant excess of certain medical conditions, the information will be verified by a review of participants' medical records.

The study is planned to begin in 2003, with data analyzed and results reported in early 2005.

Studies Based in the Vaccine Healthcare Center Network

CDC reported plans for three studies to be conducted through the VHC Network. The VHC Network is a collaboration between DoD and CDC to address issues of safety and acceptability of vaccines within the military immunization health care system. The first VHC was established at Walter Reed Army Medical Center in Washington, D.C., in September 2001. Plans call for a total of 10 to 12 VHCs to be opened over the next 5 years.

The goals for the network are to serve as a platform for studies of vaccine-related adverse health events and to enhance the immunization-related health care of military personnel. Concerns related to AVA will be the initial focus of these activities, but the VHC Network is expected to address issues related to other vaccines as well.

The three study proposals provided to the committee replicate, using observational studies in a military population, certain components of CDC's human clinical trial. Specifically, these studies will examine (1) the effects of the route of AVA administration on local adverse events, (2) the effect of AVA on health-related quality of life, and (3) the effect of hormonal phase on the occurrence of adverse events in women receiving AVA. The proposal notes that these studies will complement the human clinical trial by overcoming some of its limitations, in particular, the trial's low statistical power to test some risk-factor associations and the need to wait until the completion of the study (43 months) to perform some of the analyses. Initiation of these studies depends on resumption of routine administration of AVA to military personnel scheduled for deployment to certain areas.

Enhanced Signal Detection and Hypothesis Testing for Adverse Events Following Anthrax Vaccination

CDC plans to analyze data from VAERS and DMSS to identify signals of adverse events that might be associated with receipt of AVA. These analyses are to be performed using methods of automated exploratory data analysis referred to as data mining. Signals that are identified will be investigated further using additional data from DMSS to test for evidence of a possible causal association.

VAERS is the nation's principal system for collecting spontaneous reports of adverse events following the use of any vaccine licensed in the United States. It is jointly administered by CDC and FDA. DMSS is a system of DoD-wide databases of health-related information, including records for inpatient and outpatient care, and is coordinated by the Army Medical Surveillance Activity (AMSA). CDC is entering into a formal collaboration with AMSA that will establish an Analytic Unit based at AMSA that will conduct the analyses of DMSS data. This unit was to be established by August 1, 2002. Other collaborators include FDA and the DoD's Anthrax Vaccine Immunization Program.

Possible Role of Aluminum Hydroxide Adjuvant

CDC identified several possible research questions that might be investigated concerning the possible role that the aluminum hydroxide adjuvant in AVA might play in adverse events following vaccination. No study proposals or protocols had been developed at the time the materials were submitted to the committee.

ACCEPTABILITY

CDC's stated objectives for the acceptability component of its anthrax vaccine research program are displayed in Box 3-3.

Two survey-based studies are planned by CDC to address issues related to the acceptability of the anthrax vaccine and vaccines more generally.

BOX 3-3
CDC Objectives for Research on the Acceptability of the Anthrax Vaccine

- Knowledge, attitudes, and beliefs (KAB) surveys, a patient satisfaction survey, and other assessment tools will be developed and used to identify concerns about anthrax vaccination among military vaccine recipients. Research partners will include the DoD, the VHC Network, and the Research Triangle Institute (RTI).
- In collaboration with AVIP, VHC Network, and others, knowledge gained from the KAB surveys and the efficacy and safety studies will be used to:
  - Develop, promote, and provide training that will optimize and standardize procedures and quality assurance practices for the administration of AVA.
  - Develop strategies and training materials to help improve the acceptability of AVA and military immune readiness, in general.
- Train NIP Hotline and other CDC Hotline personnel to respond effectively to military and public questions and concerns about AVA.
- A repeat KAB survey and other assessment tools will be used after education and training interventions to measure changes in KABs and impact of interventions.

SOURCE: CDC, 2002c, p. 14.

Survey of Knowledge, Attitudes, and Beliefs Regarding the Anthrax Vaccine Among Military Personnel

CDC plans a large survey to assess the knowledge, attitudes, and beliefs of military personnel and military health care providers regarding AVA. Two phases of focus group meetings are planned. These will be followed by representative surveys of the military population at two different time points to provide an understanding of the factors influencing perceptions of anthrax vaccine safety and efficacy and to inform the development of appropriate educational materials. CDC has contracted with Research Triangle Institute (RTI) to design and implement the survey, which will gather information from a representative sample of the U.S. military's active duty and reserve populations. The baseline survey is planned to take place in early 2003, with a follow-up survey anticipated in 2005. Data analysis and reporting will take place in 2006.

Survey of Civilian and Military Health Care Providers Regarding the Anthrax Vaccine and the Reporting of Possible Vaccine-Associated Adverse Events

This study is planned to obtain nationally representative data on the knowledge, awareness, attitudes, and practices of both military and civilian health care providers regarding the reporting of adverse events following immunization to VAERS. It is also intended to obtain information from providers about their general knowledge of and attitudes about anthrax vaccination. Information obtained from the study will be applied to the development of appropriate vaccine benefit and risk communication materials, including educational and promotional materials targeted to providers regarding anthrax vaccine safety and reporting of adverse events. CDC also anticipates gathering information from this study's participants that might be used to improve VAERS from the reporter's perspective. The study will be carried out via a mail-out survey designed and administered through a contract with RTI. The survey is planned for early 2003, with analysis and reporting of data completed later that year.

In the chapters that follow, the studies described briefly in this chapter are presented in greater detail, along with the committee's evaluation and recommendations regarding each study. Chapter 7 provides the committee's assessment of the research program as a whole.

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4

Proposed Studies on the Efficacy of the Anthrax Vaccine

A critical aspect of the congressional mandate to the Centers for Disease Control and Prevention (CDC) concerns the efficacy of the current licensed anthrax vaccine, Anthrax Vaccine Adsorbed (AVA). The congressional charge explicitly calls for research aimed at determining immunologic correlates of protection and documenting vaccine efficacy, and at optimizing the vaccination schedule and the route of administration of the vaccine to assure efficacy while minimizing the number of doses required and the occurrence of adverse events.

Efficacy generally refers to the ability of a product to achieve its desired effect under ideal conditions, such as the human clinical trial and the controlled animal experiments planned by CDC. Efficacy is relative, not absolute. The protection provided by a vaccine can be influenced by factors that include the host response, the dose of exposure, the route of entry into the body, and the strain of the pathogen.

The set of studies being undertaken by CDC must examine immunogenicity as well as efficacy. *Immunogenicity* is the degree to which a substance is capable of producing immunity or evoking an immune response.[1] Immunogenicity must be used as an endpoint in human studies of the anthrax vaccine because it is unethical to expose human beings to anthrax spores to directly evaluate the efficacy of an anthrax vaccine. Parallel studies of the protection provided by the vaccine in animals that are experimentally challenged with anthrax spores will be necessary to link the human immune responses with direct evidence of the vaccine's efficacy.

OBJECTIVES AND CRITICAL RESEARCH QUESTIONS FOR CDC RESEARCH ON THE EFFICACY OF THE ANTHRAX VACCINE

CDC's stated objectives for the efficacy component of its anthrax vaccine research program are displayed in Box 4-1. The critical research questions related to efficacy are shown in Box 4-2.

The committee found CDC's research objectives and critical research questions regarding the efficacy of the anthrax vaccine to be generally complete and appropriate. In the committee's view, the question concerning the level of circulating antibody that protects an unvaccinated macaque from anthrax is a crucial one. The committee is concerned that CDC assigned this question a lower priority than the others and has planned no study to address it. This issue is discussed at length later in this chapter.

Several of the other research questions listed by CDC will be only partially addressed by its planned studies. The question of how gender affects the immune response will be addressed in the human clinical trial to the extent that the enrollment of women is successful. Similarly, because of limited statistical

[1] *Dorland's Illustrated Medical Dictionary*, 28th ed., s.v. "immunogenic."

power, it is unlikely that the study will be able to determine other potential risk factors for any differences in immune response to AVA. Larger numbers of participants would be needed to account simultaneously for age and other immune effectors such as illness or nutritional status. The role of immune memory in protection is not likely to be sufficiently addressed by the B-cell studies planned, which focus unnecessarily on cellular as opposed to humoral factors. Finally, the proposed studies will not fully answer the question of which components of AVA contribute most significantly to protection because there is no plan to evaluate individual components in AVA; the protective effects of AVA are known to be due primarily to an immune response to protective antigen (PA).[2]

BOX 4-1
CDC Objectives for Research on the Efficacy of the Anthrax Vaccine

A. Assess AVA efficacy in humans immunized with AVA by measuring immune responses identified as protective in efficacy objective B (animal studies). Immune markers of protection will be evaluated by varying the number of priming shots and the route of administration.

B. Assess AVA efficacy in animals immunized with serial dilutions of AVA and challenged with live, inhaled anthrax spores.

C. Use blood samples from the subjects in the clinical trial and in animal studies to identify immune correlates of protection and validate laboratory studies to measure them.

SOURCE: CDC, 2002e, p. 10.

BOX 4-2
Critical Research Questions Regarding the Efficacy of the Anthrax Vaccine, as Identified by CDC

- What are the correlates for protection against inhalational anthrax?
- When is protection achieved, and how long does it last?
- Are enzyme-linked immunosorbent assay (ELISA) and toxin neutralizing antibody assay (TNA) the most appropriate measurements of immune response to AVA?
- How does gender affect immune response to AVA?
- What are important risk factors for lowered immune response to AVA?
- How can we bridge from animal challenge data to predict likelihood of survival in AVA-vaccinated humans?
- What is the role of circulating antibody in protection?
- What is the role of immune memory in protection?
- What is the antigenic make-up in the AVA lots used for CDC studies?
- What is the quantity of PA [protective antigen] in the AVA lots used for CDC studies?
- Which components of AVA contribute most significantly to protection against anthrax?
- What is the basis, if any, for the current series and can that series be reduced to a more practical number?
- Is the vaccine equally efficacious or immunogenic when administered intramuscularly?
- What level of circulating antibody protects an unvaccinated macaque from anthrax?

SOURCE: CDC, 2002f.

[2] Efficacy studies in laboratory animals have indicated that PA must be present in a cell-free anthrax vaccine or produced by a live vaccine to achieve protection (Ivins et al., 1986, 1992, 1998; discussed in IOM 2002).

ANTHRAX VACCINE ADSORBED: HUMAN REACTOGENICITY AND IMMUNOGENICITY TRIAL TO ADDRESS CHANGE IN ROUTE OF ADMINISTRATION AND DOSE REDUCTION (HUMAN CLINICAL TRIAL)

This study is intended to compare the immunogenicity and reactogenicity of AVA when given under the currently licensed regimen—subcutaneous (SQ) administration of six primary doses of vaccine (at 0, 2, and 4 weeks and 6, 12, and 18 months) and annual booster doses—with the immunogenicity and reactogenicity of the vaccine when a reduced number of doses are given intramuscularly (IM) (CDC, 2002a,h). The components of the study related to immunogenicity are discussed here; those related to reactogenicity are reviewed in Chapter 5.

The study follows up the findings from a pilot study carried out at the U.S. Army Medical Research Institute of Infectious Diseases indicating that concentrations of anti-PA antibodies measured 2 weeks after the administration of two doses of AVA given 4 weeks apart (either IM or SQ) were comparable to those measured 2 weeks after the administration of three doses (SQ) given 2 weeks apart (the licensed dosing schedule) (Pittman, 2002). Taking into account these pilot data, CDC proposes two hypotheses related to immunogenicity for the Human Clinical Trial:

1. AVA administered by the IM route elicits antibody responses that are not inferior[3] to those achieved by the SQ administration.
2. AVA administered by the IM route and with fewer doses elicits antibody responses that are not inferior to those achieved by the currently licensed schedule. (CDC, 2002a,h)

Study Design

The study is designed as a prospective, randomized, double-blind,[4] placebo-controlled clinical trial to be conducted over a period of 43 months at five sites in the United States. The study population will consist of 1,560 healthy civilian adult men and women between the ages of 18 and 61 years. The study will be open to anyone meeting the eligibility criteria, but recruitment efforts will focus on groups for whom AVA vaccination for bioterrorism preparedness has been considered, including emergency first responders, federal responders, and medical practitioners. The size of the study population reflects an allowance for up to 50 percent attrition over the course of the study.

Study participants will be randomly assigned to one of six study groups of 260 persons each (see Table 4-1). One study group will receive AVA under the currently licensed regimen (SQ administration of six doses over 18 months, followed by two boosters a year apart). A placebo group will receive eight injections of sterile saline; half of the group will receive SQ injections and half will receive IM injections. In the four other study groups, participants will receive either four, five, seven, or eight IM doses of AVA. The study plan calls for all vaccine doses to come from AVA Lot FAV063, manufactured by BioPort Corporation as a "post-renovation qualification lot" (CDC, 2002a, p. 61). Participants who receive fewer than eight doses of AVA will receive an injection of the saline placebo in place of an omitted dose of AVA.

To evaluate the immunogenicity of AVA in each study group, each participant will have a total of 16 blood samples drawn at specified times over the course of the study, including a sample that will be drawn before the first vaccination. Serum from the blood samples will be assayed for total levels of immunoglobulin G (IgG) antibodies to PA using a standardized and validated enzyme-linked immunosorbent assay (ELISA). The study's primary endpoints for immunogenicity will be a fourfold rise in antibody

[3] For FDA to approve a modification of the AVA label regarding the route of administration or the schedule of doses, data must show that the modified route of administration and dosing schedule are at least as immunogenic as (non-inferior to) the currently licensed regimen.

[4] Unblinded staff will prepare and administer the vaccine or placebo, but CDC staff, the investigators monitoring and analyzing immunogenicity and reactogenicity, and the participants will remain blinded to study group assignment.

TABLE 4-1 Schedule of Injections for Study Groups in the Human Clinical Trial of Alternative Routes of Vaccine Administration and Schedules of Vaccine Doses

Study Group	No. and Route of Injections	n	Timing and Content of Injections: Week 0	Week 2	Week 4	Month 6	Month 12	Month 18	Month 30	Month 42
1	8 SQ	260	AVA	AVA	AVA	AVA	AVA	AVA	AVA	AVA
2	8 IM	260	AVA	AVA	AVA	AVA	AVA	AVA	AVA	AVA
3	7 IM	260	AVA	S	AVA	AVA	AVA	AVA	AVA	AVA
4	5 IM	260	AVA	S	AVA	AVA	S	AVA	S	AVA
5	4 IM	260	AVA	S	AVA	AVA	S	S	S	AVA
6a	8 IM	130	S	S	S	S	S	S	S	S
6b	8 SQ	130	S	S	S	S	S	S	S	S

NOTE: AVA: Anthrax Vaccine Adsorbed; S: saline placebo; SQ: subcutaneous; IM: intramuscular
SOURCE: Adapted from CDC, 2002a, p. 56.

titer and in antibody concentration. In a subset of the serum samples, an in vitro toxin neutralization assay (TNA) will be used to measure the functional activity of anti-AVA antibodies. These assays are also the focus of effort in the studies of the immune correlates of protection (ICP).

Samples from three time points in the clinical trial will be used to examine the kinetics of the immune response to AVA, and samples from a subset of participants will also be used for additional tests in studies of the correlates of protection and of immunogenetics.

For the study of immune kinetics, blood drawn 3 to 15 days following the vaccinations at 6 months, 30 months, and 42 months will be assessed for PA-specific antibody titer, concentration of anti-PA IgG, and TNA titer. (Participants will be randomly assigned to return to the study site in a manner that distributes their blood sampling evenly over the 3–15 day period.) The rate of increase in the geometric mean concentration (GMC) of anti-PA IgG will be compared among the groups, based on the first post-injection day on which a fourfold rise in antibodies and TNA titers occurs. A complementary study of antibody kinetics in nonhuman primates (NHPs) will take place in parallel as part of the NHP Vaccine Dose Ranging Study.

The study of immunogenetics is planned to test the hypothesis that genetic polymorphisms of the human leukocyte antigen system (HLA) significantly influence the immune response to AVA (CDC, 2002h). The substudy will be carried out by the Mayo Clinic and Foundation. A random sample of 344 participants from the clinical trial will serve as the population for both this study and the Immune Correlates of Protection Study described later. Approximately 275 of these subjects are expected to receive AVA; the remainder will receive only the saline placebo. HLA typing will be carried out on blood samples drawn at the start of the study before vaccination. This substudy has the following aims:

1. To estimate the association between specific alleles of class I HLA alleles (A, B, C) and the immune response following anthrax immunization in human subjects
2. To estimate the association between specific alleles of class II HLA alleles (DRB, DQA, DQB, DPA, and DPB) and the immune response following anthrax immunization in human subjects
3. To estimate the effects of genetic variation across the class I and class II HLA alleles and the immune response (circulating antibody level and anthrax-specific lymphoproliferative responses) following anthrax immunization in human subjects (CDC, 2002h, pp. 5–6)

Planned Analyses

The study protocol specifies that the primary analyses for immunogenicity will be conducted using the participants who can be evaluated "according to protocol,"[5] based on adherence to the schedules for injections and blood sampling. An intent-to-treat analysis will also be conducted, using all available data for each participant regardless of compliance with the study protocol. Missing data will be assumed to be missing at random. With the intent-to-treat analysis, investigators can assess whether deviations from the protocol were vaccine group-related and led to bias in the results. A third set of immunogenicity analyses will be done to complement the according-to-protocol and intent-to-treat analyses to assess responses among participants who receive all doses of vaccine, regardless of whether a protocol violation has occurred.

For each blood sampling, the proportion of participants with a fourfold rise in anti-PA IgG antibody titer will be summarized. The proportion of participants with a fourfold rise in antibody titers in each of the study groups under the alternative regimens will be compared with the proportion in the study group receiving the vaccine under the licensed regimen to determine if the alternative regimens are at least as immunogenic as (i.e., non-inferior to) the licensed regimen.

GMCs of anti-PA antibody for each study group will also be calculated and summarized for each blood draw. The significance of differences in GMCs between the licensed and alternative regimens will be assessed using mixed-model analysis of variance (ANOVA) procedures. The null hypothesis that a modified route and dose schedule is inferior will be rejected in one-sided tests if the upper 97.5 percent confidence limit for the GMC ratio (reference group:study group) is <1.5 and if the ratio of fourfold responders is <1.12. Sample sizes to achieve 80 percent power with a 95 percent one-sided hypothesis test were calculated using variance estimates from a pilot study of changes in the route of administration and dosing schedule and allowance for a 50 percent attrition rate. CDC will contract with statistical experts to examine deviations from the protocol in the form of dropouts, noncompliance, and loss to follow-up and to devise appropriate analyses (CDC, 2002h).

Committee Comments

On the whole, the committee found that the study, as described in the protocol, provides an appropriate basis for comparing the immunogenicity of SQ and IM administration of AVA, and for comparing the immunogenicity of the licensed schedule of SQ doses with regimens that use fewer IM doses. The criteria for analysis of non-inferiority appear to be appropriate. The study should provide information that is valuable both for optimizing the administration of the currently licensed anthrax vaccine and, when carried out in conjunction with the NHP challenge studies, for the development and licensure of new anthrax vaccines. Both of these needs were emphasized by the Institute of Medicine (IOM) committee that recently reviewed the efficacy and safety of AVA (IOM, 2002), and they are of greater public concern following the deaths and nonfatal cases of anthrax that occurred as a result of the bioterrorist incidents in the fall of 2001.

The committee also notes that the use of vaccine from a lot manufactured following the completion of the renovation of the BioPort facilities will provide an opportunity to evaluate the immunogenicity of the newly manufactured vaccine, as was recommended in the recent IOM report (IOM, 2002).

Finding: As described in the study protocol, the human clinical trial is generally responsive to the congressional mandate and to important research needs for determining immunologic

[5] According-to-protocol analysis includes in its calculations only those study participants who fulfill all entry criteria and complete the trial according to its protocol. Intent-to-treat analysis includes data from all study participants regardless of whether every person enrolled or randomly assigned to a group completed the trial. In randomized controlled trials, the intent-to-treat approach preserves the similarity between different treatment groups that randomization provides. Intent-to-treat analysis accounts for participants who are lost to follow-up or unable to complete the study protocol. Failure to include all participants may permit a bias in the results if non-completion of the trial is related in any way to the treatment or the vaccine tested (Altman et al., 2001; *Health Technology Assessment News*, 1999).

correlates of protection, documenting the immunogenicity of AVA, and optimizing the vaccination schedule and routes of administration of AVA.

Since the release of its interim report in July 2001 (IOM, 2001), the committee has received more detailed plans regarding the substudy to assess HLA genetic polymorphisms. CDC's rationale for the inclusion of this effort is that it will extend work previously carried out with measles vaccine and other vaccines. The earlier work indicated that HLA genetic polymorphisms significantly influence antibody levels following receipt of live measles vaccine (Hayney et al., 1996, 1998; Poland et al., 1998; St. Sauver et al., 2002). With analysis of samples from this prospective clinical trial of AVA, the investigators propose to extend their work to a vaccine against a toxin-producing pathogen to further evaluate the generalizability of their earlier findings.

The committee is not persuaded that this substudy contributes meaningfully to the research plan for AVA. There is good evidence that immune response is directed in part by genetic background, but large sample sizes are usually needed to associate differences in response with differences in genetic characteristics. The substudy appears adequately powered to address its specific aims of estimating the association between specific alleles of class I or II HLA alleles and the immune response to AVA or of estimating the associations between genetic variation across class I and class II alleles and changes in the immune response. However, it does not appear to be adequately powered to be able to take into account demographic variables such as sex and race, which also affect immune response. Further, at least two different endpoints are proposed: (1) antibody levels to assess the humoral response, and (2) a lymphoproliferative assay and perhaps other measures to assess the cellular response. The adjustments that would be necessary to allow for multiple comparisons are not described. While the question of the relationship between HLA alleles and immune response may have some broad scientific interest, it warrants only low priority among CDC's studies of the safety and efficacy of AVA.

Finding: The HLA substudy experiments as described are not critical to resolving the concerns regarding the safety and efficacy of AVA. As part of the CDC anthrax vaccine safety and efficacy research program, the studies should be considered of low priority.

The success of the study will depend, in part, on recruiting and retaining an adequate number of participants. The study protocol comments on plans for recruiting participants and notes that up to 50 percent of those who begin the study might be lost. The committee urges that CDC and the participating centers ensure that those interested in participating in the trial fully understand the demands of the study, in terms of both the vaccination schedule and the time commitment involved. The plan to assume that missing data are missing at random should be supported by the collection during the course of the study of the information necessary to test that assumption.

Even if efforts are made to minimize loss to follow-up and noncompliance, CDC should be taking steps to ensure appropriate analysis of incomplete data. In the interim report, the committee urged careful consideration of statistical methodologies for analysis of the data from the human clinical trial, noting that the intent-to-treat analysis may be less appropriate for a clinical trial of a vaccine to be used in a military setting than for vaccines intended for general civilian use (IOM, 2001). Appropriate analysis of the clinical trial data is crucial to gaining approval from FDA for any change in the route of administration of AVA or in the schedule of doses required. The committee urges continued consultation with experts in the analysis of data from clinical trials with significant loss to follow-up or noncompliance. In addition, CDC should be consulting with FDA on this matter. Although some sections of the protocol reviewed by the committee indicate that consultation with FDA has taken place, no specific mention is made of consultation with FDA on the appropriateness and acceptability of these particular analyses. The committee wishes to emphasize that concurrence from FDA on the appropriateness of the analysis is imperative.

Recommendation: CDC should consult with FDA and receive their approval regarding the type of analysis (according to protocol, intent to treat, or other) that will provide appropriate

support for a change in the labeling of AVA regarding the route of administration and the number of doses required.

NONHUMAN PRIMATE VACCINE DOSE RANGING, IMMUNOGENICITY, AND CHALLENGE TRIAL

The NHP study is intended to provide information from experiments with rhesus macaques about the relationship between immune responses developed from vaccination with AVA and protection from aerosol challenge with anthrax spores (CDC, 2002b,i). Based upon the assumption that similar immune responses in human and nonhuman primates will be similarly protective, the study will help provide information about the protection that AVA (and future anthrax vaccines) provides to humans.

CDC has planned the study to address the following objectives:

1. Using dilutions of AVA to induce a spectrum of immune responses, identify immune correlates of protection against challenge at 12, 30, and 42 months after initial immunization of rhesus macaques (*Macaca mulatta*)
2. Bridge these data to immune response data from similar time points in the human trial to potentially identify surrogates of protection that reflect the correlates of protection in macaques
3. Provide survival (and potentially immunological) data from macaques immunized intramuscularly with three doses of AVA that will support the objectives of dropping doses and changing the route of administration of AVA of the human clinical trial (CDC, 2002b, p. 14; 2002i, p. 1)

Study Design

Rhesus macaques randomly assigned to receive a three-dose series (0, 4 weeks, and 26 weeks) of AVA at full dose or fixed dilutions (1:5, 1:10, 1:20 or 1:40) of the full dose will be challenged at 12, 30, or 42 months after vaccination with approximately 200 times the amount of anthrax spores that would be expected to kill half the animals. Vaccinations with different dilutions of AVA are expected to induce different levels of immune response in the macaques. Rates of survival after lethal challenge of these animals will provide data to describe a relationship between immune response and survival. The current study design represents a modification of the original plan, which had as its objective to identify an "appropriate" dose of AVA for use in macaques.

In Phase I of the study, begun March 2001, five groups of macaques (10 AVA-vaccinated animals and two saline-vaccinated controls per group) received IM injections of either a full dose of AVA or of dilutions of 1:5, 1:10, 1:20 or 1:40 at 0, 4, and 26 weeks. Preliminary data indicate that the vaccine dose dilutions elicit dose-dependent gradations in humoral and cellular immune factors (anti-PA IgG, toxin neutralization, and T-cell proliferation) that are expected to be important for protection (CDC, 2002b). To minimize unnecessary animal deaths, investigators will use the results of an aerosol challenge of the animals in the 1:20 dilution group at 54 weeks (to have taken place March/April 2002) as the basis for deciding which challenges to administer to additional groups of macaques (see CDC, 2002b for details, pp. 16–22, p. 42). Blood samples taken at specified intervals following vaccination and following challenge will provide material for analysis of immune factors that may play a role in protection from challenge.

The study will be carried out at Battelle Memorial Institute, Emory University Vaccine Center, and the Meningitis and Special Pathogens Branch of the National Center for Infectious Diseases at CDC. Most of the macaques involved in the study (132 for the entire study) are located at Battelle, but 33 animals, divided among three vaccine-dilution groups (undiluted, 1:10, and 1:20) of 10 animals each and 3 control animals, were to be vaccinated at Emory University in June 2002. Blood specimens from these animals will be collected at Emory during the first 30 months following the start of vaccination. The animals will then be transported to Battelle for an aerosol anthrax spore challenge at 30 months. Under some

of the scenarios for survival and challenge, results from challenges of animals based at Battelle will lead to certain of the animals housed at Emory being removed from the study rather than being challenged (CDC, 2002b).

CDC plans to use logistic regression for its primary analyses, as well as alternative approaches such as generalized additive models, classification and regression trees, and multiple adaptive regression trees. Genuine predictive performance measures will be used to assess the predictive performance of methods used for the study. Power calculations awaited additional refinement at the time the protocols were provided to the committee.

The NHP studies will require the use of two different lots of AVA. The first 60 animals were vaccinated in March 2001 with AVA from Lot FAV048B. Future doses will come from Lot 063 to be consistent with the "postrenovation" lot of vaccine that will be used in the human clinical trial. While it would have been desirable to use only one lot for all of the studies, the postrenovation lot was not yet available at the start of the NHP studies.

The laboratory assays for this study as well as those for the human clinical trial and the study of immune correlates of protection have all been reviewed by the Laboratory Issues panel, one of the expert consultation panels convened by CDC in response to recommendations from this committee in the interim report.

Committee Comments

As described in the summaries and research protocols provided to the committee, the NHP study is an appropriate and crucial aspect of the congressionally mandated research to document the efficacy of AVA and to determine immune correlates of protection. Because challenge of humans with lethal agents such as anthrax is not ethical, animal experiments are necessary, and the rhesus macaque is an appropriate model for such studies (discussed in IOM, 2002).

The current approach to the NHP study, significantly modified since it was first presented to the committee, promises to meet the need for additional information about protective levels of antibody or other immune factors. Such information can be useful not only in optimizing the dose schedule for AVA, but also in evaluating the efficacy of new anthrax vaccines under development.

Finding: The committee finds that the nonhuman primate studies that have been proposed as a means to provide information about the efficacy of AVA are well designed and responsive to the congressional mandate and to important research needs. The information gathered will inform and influence the development and licensure of new protective antigen-based anthrax vaccines.

Two lots of vaccine, one of them produced before the renovations of the manufacturing facility and one produced "postrenovation," will be used in the NHP study. The research plan indicates that detailed analyses of the vaccine composition are to be carried out by a contract laboratory. It is important that there be a detailed comparison of the antigen content of the vaccine from the two lots used in the study. The characterization of the vaccine lots should be described in formal protocols, which should be reviewed by the Laboratory Issues Panel.

Recommendation: Careful characterization of the vaccine lots used in the clinical trial and nonhuman primate studies is crucial. Protocols for this work should undergo review by the expert consultative panel convened for laboratory issues.

The protocol describes an approach of "retiring" some animals without anthrax aerosol spore challenge based upon results of challenges of animals immunized with AVA at 1:20 dilution. The protocol provided by CDC in February 2002 does not describe the analytical approaches planned to account for the issues of missing data that will be raised by retiring selected animals. Investigators should consult with

the expert consultation panel on statistics to arrive at appropriate methods for handling missing data due to retiring animals or other causes.

The protocol provided to the committee lacked detail regarding plans for statistical analysis for the NHP studies. Given the complex experimental design, it is imperative that CDC receives expert input in devising their analytical plan.

Recommendation: CDC should consult with the Statistics Panel for expert guidance on analyses of data from the nonhuman primate studies, including devising appropriate methods for handling missing data.

The research protocols and other materials submitted to the committee for review do not describe plans for any passive protection studies. Passive protection studies are experiments in which serum from immunized animals or humans (i.e., immunoglobulin) is administered to naïve animals who are then challenged so that the level of protection provided by the circulating antibody from the immunized animal or human can be evaluated. Because immunoglobulin has a limited half-life in animals, it is necessary to evaluate the protection it affords during a limited period of observation appropriate to this half-life. Although CDC cites identifying the level of circulating antibody required to protect an unvaccinated macaque from anthrax as a critical research question, it assigns the question a low priority.

The committee, however, considers passive protection studies to be an essential component of a research program on AVA. While studies of active protection can be extremely useful, they do not permit identification of a specific protective factor that might be used as a proxy for protection in clinical circumstances. Passive protection studies would make it possible to demonstrate unequivocally that the immune factors (e.g., antibody to PA) present in the serum of vaccinated animals afford protection. They can also show whether immune factors generated in humans are protective in animals, providing additional information for bridging data from animals to humans. The studies can be used to directly determine the amount of circulating antibody required for protection from inhalational challenge in the absence of immunologic memory. They can also be used to estimate the level of circulating antibody to PA that must be reached before antibiotic prophylaxis can be discontinued. In addition, passive protection studies can provide information about the expected time frame (how quickly and for how long) for protection following immunization with AVA or more modern PA-based vaccines. These experiments are also essential to better characterize the dosage of therapeutic immune globulin necessary to prevent disease in people who may have been exposed to anthrax spores or to treat patients with anthrax disease**.**

Finding: Passive protection studies are important for improving understanding of the mechanism(s) of the efficacy of AVA and can help to address practical issues related to the management of anthrax disease.

Recommendation: CDC should conduct passive protection studies as part of its anthrax vaccine safety and efficacy research program.

The distribution of anthrax spores through the postal system in the fall of 2001 made it clear that additional information is needed about the protection afforded by vaccination with AVA against different challenge doses of aerosolized spores of *B. anthracis.* CDC reported that different doses of anthrax challenge were not included in the protocol for the NHP studies because doing so would introduce more variables than could be accommodated with a study of the size they have planned (CDC, 2002g).

The committee urges CDC to help address this research gap. The passive protection studies recommended above will help determine an optimal amount of antibody or other correlate of protection to protect against a challenge dose of a particular size. Once a protective level of antibody (or other correlate of protection) has been established, the effect of varying the size of the inoculum should be evaluated.

Finding: Research is needed to understand better the effect of the size of the challenge dose on the protection afforded by AVA.

Recommendation: CDC should support or conduct research on the effect of the size of the challenge dose on immunity provided by vaccination with AVA.

IMMUNE CORRELATES OF PROTECTION AGAINST INHALATIONAL ANTHRAX STUDIES

Closely related to the NHP studies described above are studies of the immune correlates of protection against anthrax. These studies are planned to identify components of the rhesus macaque humoral and cell-mediated immune responses to AVA that correlate with protection against aerosol challenge by virulent *B. anthracis*. The ICP studies will develop and apply a panel of immunologic assays to test the hypothesis that "one or more measurable immunological markers of protection can be identified in a non-human primate model of inhalation infection with *B. anthracis* spores and that one or more of these measurable immunological markers are identifiable in AVA vaccinated humans" (CDC, 2002j, p. 1). The goals of the ICP studies are listed in Box 4-3.

Planned Analyses

The ICP studies will be carried out at three main sites: Battelle Memorial Institute, Emory University Vaccine Center, and the Meningitis and Special Pathogens Branch of the National Center for Infectious Diseases at CDC. In addition, the Centre for Applied Microbiology and Research (CAMR) at Porton Down, United Kingdom, will develop and apply a range of standardized ELISA and other assays under subcontract to Battelle (CDC, 2002d, Appendix 8.2).

Experience with aluminum adjuvants suggests that "vaccination with AVA will favor a Th-2 type immune bias manifest in part as a strong humoral IgG_1 antibody response" (CDC, 2002j, p.7). Therefore the emphasis in the ICP studies is on the description and quantification of antibody responses to PA, lethal factor (LF), and edema factor (EF), using quantitative anti-PA IgG ELISA and TNA. The same assays are also being used in the Human Clinical Trial as primary endpoints for evaluating immunogenicity.

Sera from all of the NHPs and from a subset of the participants from the human study will also be evaluated with more detailed analyses of the anti-PA IgG antibody subclasses; anti-PA IgM, anti-PA IgA and anti-PA IgE; as well as anti-LF IgG and anti-EF IgG. Additional assays will evaluate neutralization of the enzymatic properties of LF and EF (an endopeptidase and adenylate cyclase, respectively), neutralization of anthrax lethal toxin at different stages in the anthrax toxin complex formation and the ability of anti-AVA antiserum to promote opsonophagocytosis.

To learn as much as possible about the wider immunologic response to AVA, the ICP studies will also include an analysis of factors related to cellular immune response. Cell-mediated immune response (CMI) to AVA is important because without CD4+ T-cell help, protective humoral immunity against toxemia will not be generated (CDC, 2002j). The study will therefore include comprehensive descriptive and quantitative analyses of immune-cell responses to AVA administered at different dilutions. Plans call for the analysis of NHP samples at both the Battelle and Emory sites; some of the samples from the human trial may be analyzed as well (CDC, 2002j).

Committee Comments

In general, the committee found the ICP studies to be an appropriate and important component of the effort to evaluate the efficacy of the anthrax vaccine. While qualitative correlations have been established between antibodies to PA and protection in animal models, quantitative correlations remain to be determined. The proposed studies should provide the additional information needed to do so. This information can be useful not only in gaining a better understanding of the mechanism and duration of protection provided by AVA, but also for licensing newer PA-based vaccines under development.

One important contribution anticipated from the ICP studies is the development and standardization of assays necessary for research in this area. The recent IOM report on the anthrax vaccine (IOM, 2002)

included a recommendation for efforts to standardize an assay for quantitation of antibody levels that can be used across laboratories carrying out research on anthrax vaccines. The ICP studies will use anti-PA ELISA and TNA assays developed at the National Center for Infectious Diseases at CDC, as well as additional assays to be developed and validated at CAMR as part of the research project.

Finding: The committee strongly supports the use of validated assays that can be standardized across the field of anthrax vaccine research. CDC's development and validation of such assays will provide an important contribution in this regard.

Recommendation: CDC should give high priority to standardization of assays that can be used across laboratories conducting research with anthrax vaccine.

The committee found the many goals outlined by CDC for the ICP studies (Box 4-3) to vary widely in scientific value. The goals of quantifying the IgG response to PA and other anthrax antigens, quantifying the lethal toxin response, describing the anti-PA IgG subclass profiles in vaccinees, and describing the maturation of anti-PA IgG avidity in AVA vaccinees are, in the committee's view, important and necessary. The remaining goals described by CDC are viewed as of lower priority. While examination of a panel of immunologic responses is interesting, it is not likely to provide important new insights regarding AVA's mechanism of protection.

The committee is particularly dubious of the value of the proposed efforts to characterize a role for AVA-specific CD4+ T helper cells in the anamnestic anti-PA antibody response to in vitro challenge. The protocol does not make clear how the in vitro data could be correlated with responses in vivo. Similarly, there is no clear plan for correlating the count of bone marrow plasma cells to anamnestic immune re-

BOX 4-3
Goals of Assays of Immune Correlates of Protection, as Specified by CDC

- Quantify the IgG response to anthrax toxin PA and other selected anthrax antigens.
- Quantify the anthrax lethal toxin (PA+LF) neutralization response.
- Describe the anti-PA IgG subclass profiles in AVA vaccinees.
- Describe the maturation of anti-PA IgG avidity in AVA vaccinees.
- Determine the ability of anti-AVA antisera to promote opsonophagocytosis.
- Quantify the PA-specific proliferative responses of circulating T-cells.
- Describe and quantify selected cytokine mRNA synthesis and protein secretion patterns in circulating T-cells following in vitro stimulation with PA.
- Characterize the magnitude and duration of T-cell (CD4+) and B-cell components of immune memory to AVA vaccination.
- Enumerate the circulating PA-specific memory CD4+ T-cells at selected time points during and post immunization.
- Enumerate the T-cell-dependent, PA-specific, bone-marrow plasma cells (NHPs only) and circulating antibody-secreting memory B-cells (NHPs and humans) at selected time points during and post immunization.
- Identify CD4+ T-cell-stimulating epitopes in the PA protein in order to track PA-specific memory T-cells and a protective immune response against anthrax. This may help with the longer-term goal of identifying candidate DNA vaccine epitopes.

SOURCE: CDC, 2002j, pp. 2–3.

sponse outcome. Finally, identification of the CD4+ T-cell-specific epitopes on the PA molecule is a detail of the immunologic response mechanism that does not directly apply to safety or efficacy and is not appropriate to pursue as part of CDC's research program.

The committee also had concerns about CDC's plans for certain ICP studies to be done on the 33 macaques housed at Emory. The studies to be carried out exclusively at Emory are semi-quantitative analysis of in vitro PA-specific antibody and cytokine-secreting peripheral blood mononuclear cells (PBMC). Two other assays—the quantification of the PA-specific T-cell proliferative capability in peripheral blood cells and the identification of CD4+ T-cell-stimulating epitopes and linear humoral epitopes on the PA protein—are being done in conjunction with Battelle and CDC, respectively.

Investigators at Emory also plan to carry out lymph node biopsies, bone marrow biopsies, and bronchoalveolar lavage on the 33 rhesus macaques housed there. The researchers hope to use the results of those tests to correlate immune responses occurring in tissues or organs of the macaques with their PBMC and to infer the type and magnitude of immune responses to AVA that are occurring systemically in human vaccinees (CDC, 2002c). The hypotheses to be tested are that the generation and persistence of long-lived plasma cells in the bone marrow are key determinants of long-term humoral immunity and that sustained serum antibody to vaccine antigens will correlate with the presence of antigen-specific plasma cells in the bone marrow (CDC, 2002c). An ELISPOT assay will be used to test bone marrow samples for the presence of plasma cells specific for PA, LF, and PA-LF.

According to the protocol, the analysis may provide new guidelines for the minimum number of immunizations necessary to generate long-term humoral immunity to anthrax. As noted above, however, the committee questions the extent to which these studies can contribute to addressing this research question. Studying the duration of the immune memory response is important and necessary, but such studies should focus on the duration of anti-PA antibodies and other antibodies. Thus far, only anti-PA antibodies have been shown to be related to protection in rhesus macaques.

The protocols call for the lymph node biopsies, bone marrow biopsies, and bronchoalveolar lavage to be carried out at least 12 times (CDC, 2002c). The committee acknowledges that the aim of the study is to gather as much information as possible from the macaques to be able to assist in understanding mechanisms in humans. But the tremendous number of invasive procedures to be carried out on the animals is of concern. In the absence of specific, compelling hypotheses to be tested, the extensive procedures do not appear to be adequately justified or even likely to be feasible, since the frequent administration of anesthesia and the repeated biopsies may alter the responses of interest. The proposed research is descriptive rather than hypothesis-driven and should be of a low priority.

Finding: The biopsies of lymph nodes and bone marrow and the bronchoalveolar lavage planned as part of the Immune Correlates of Protection Study require multiple invasive procedures that do not appear to be adequately justified.

Recommendation: On the basis of the information provided to the committee for evaluation, the committee recommends that the NHP studies requiring multiple samplings from biopsies of lymph nodes and bone marrow and from bronchoalveolar lavage should not be continued in their current form. If such studies can be adequately justified, they should be modified to require fewer invasive procedures.

Finding: With the exception of the biopsy and bronchoalveolar lavage studies noted above, the committee finds that the ICP studies that have been proposed as a means to provide information about the efficacy and immunogenicity of AVA are responsive to the congressional mandate and to important research needs. The information gathered will inform and influence the development and licensure of new PA-based anthrax vaccines.

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5

Proposed Studies on the Safety of the Anthrax Vaccine

The congressional mandate to the Centers for Disease Control and Prevention (CDC) for research on the anthrax vaccine includes a call for studies to examine risk factors for adverse events, including differences in rates of adverse events between men and women, and studies to optimize the vaccination schedule and administration of the vaccine to minimize the occurrence of adverse events. The materials presented to the committee by CDC describe several studies that have been proposed to respond to these aspects of the congressional mandate. This chapter summarizes the relevant components of each of these studies and presents the committee's findings and recommendations regarding each study.

The committee notes that the standard regulatory terms for any undesirable effect of a vaccine (or other biologic or drug) are *adverse event* or *adverse reaction*.[1] Adverse events can range from mild to severe or life-threatening. The standard term used by regulatory agencies to describe the characteristic profile of adverse events associated with a product is the *safety* of the product. The committee emphasizes that the safety of a vaccine or other product is relative, not absolute. In general, the term safety reflects expectations of relative freedom from, but not necessarily the complete absence of, harmful effects when a product is used prudently, considering the condition of the recipient and the health risk the product is directed against.[2]

No single set of criteria defines acceptable limits on the frequency and severity of vaccine-related adverse events. Expectations for the safety of vaccines are especially high, however. In contrast to therapeutic agents, which are given when a disease is known to be present (or at least suspected), vaccines are usually given to healthy people to protect them against pathogens that they may or may not be exposed to in the future.

Thus, the committee reviewed the studies proposed by CDC with the expectation that they should be appropriate for producing knowledge that can aid in the evaluation of suitable uses of Anthrax Vaccine Adsorbed (AVA) and of possible new anthrax vaccine formulations.

[1] An adverse event includes any undesirable condition that occurs following vaccination, whether or not it is causally linked to the vaccine. An adverse reaction is an event considered causally related to receipt of the vaccine.

[2] The definition of safety used by FDA is "the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time" (21 C.F.R. § 600.3[1999]).

OBJECTIVES AND CRITICAL RESEARCH QUESTIONS FOR CDC RESEARCH ON THE SAFETY OF THE ANTHRAX VACCINE

CDC's stated objectives for the safety component of its anthrax vaccine research program are displayed in Box 5-1. At the request of the committee, CDC also identified a set of critical research questions, shown in Box 5-2.

BOX 5-1
CDC Objectives for Research on the Safety of the Anthrax Vaccine

- To investigate potential long-term sequelae of AVA.
- To gain a better understanding about the type, frequency, and gender differences of vaccine adverse events associated with AVA.
- To evaluate the completeness and accuracy of reporting of AVA adverse events in the military and to develop and implement interventions to improve AVA adverse events reporting and surveillance.
- To assess AVA administration practices and the military immunization health care system that may impact AVA adverse events, and to enhance AVA delivery practices (quality assurance of AVA administration services in the military).
- To evaluate concerns that military personnel may have about AVA and improve their knowledge and understanding about the risk benefit of AVA and other vaccines.
- To provide AVA information, education, and communication resources to the civilian public and to military personnel in collaboration with the Department of Defense.

SOURCE: CDC, 2002d, p. 11.

BOX 5-2
Critical Research Questions Regarding the Safety of the Anthrax Vaccine, as Identified by CDC

- How does changing the route of administration affect the safety profile of AVA?
- What are the important risk factors for the development of adverse events to AVA?
- Is gender an important risk factor for the development of adverse events to AVA?
- What is the overall safety profile of AVA immunization?
- Are there any chronic health or long-term problems associated with AVA immunizations?
- Are there specific syndromes or disorders associated with AVA?
- Does hormonal phase affect the occurrence of adverse events [in women]?
- Is AVA safe for children?
- Is AVA safe for use in the elderly?
- Is AVA safe for women, with respect to reproductive health?
- What is the safety profile of AVA when administered postexposure with antibiotics?
- What is provider knowledge of VAERS and compliance with reporting to VAERS?

SOURCE: CDC, 2002e.

The committee found CDC's research objectives and research questions regarding the safety of the anthrax vaccine to be responsive to the request from Congress. The committee notes that while Congress and CDC specifically address differences between men and women in their risks for adverse events following vaccination, other demographic characteristics such as age and race may also be related to the risk for adverse events. In addition, the committee cautions that while the investigation of potential chronic or delayed sequelae of the receipt of AVA is of interest, it is a challenging research task. Identifying particular conditions in the small study population that has been proposed for this purpose and establishing a biologic basis for connecting any conditions that might be identified with the receipt of AVA would be difficult.

The research objectives and questions (and the related study proposals) concerning the reporting of adverse events and the acceptability of AVA, which go beyond the specific congressional request, are discussed in Chapter 6.

CDC has included among the critical research questions determining the safety of AVA when it is administered to children or older adults, and when it is administered in conjunction with antibiotics following exposure to anthrax spores. However, CDC gave a lower priority to these questions than to the others it listed. The committee feels these are critically important questions, although it agrees that studies in these populations should be delayed long enough to be able to take into account the findings from the human clinical trial on the optimal route and number of vaccine doses for young and middle-aged adults. Planning for future studies in children and the elderly should be flexible enough to respond to changing circumstances, including the possible availability of a newer anthrax vaccine. The committee identified persons with chronic illnesses as another population that should be studied—again, after taking into account the findings on immunogenicity and reactogenicity in healthy adults from the clinical trial and allowing for modifications in response to changing circumstances. The committee's views on the place of such studies within the CDC research program are discussed in Chapter 7.

In the remainder of this chapter, the committee reviews the specific studies that have been proposed and presents its findings and recommendations concerning those studies.

ANTHRAX VACCINE ADSORBED: HUMAN REACTOGENICITY AND IMMUNOGENICITY TRIAL TO ADDRESS CHANGE IN ROUTE OF ADMINISTRATION AND DOSE REDUCTION

This study, referred to as the human clinical trial, is intended to compare the immunogenicity and reactogenicity of AVA when given under the currently licensed regimen—subcutaneous (SQ) administration of six primary doses of vaccine (at 0, 2, and 4 weeks and 6, 12, and 18 months) and annual booster doses—with the immunogenicity and reactogenicity of the vaccine when a reduced number of doses are given intramuscularly (IM) (see CDC, 2002a,f). The components of the study related to immunogenicity are described in Chapter 4. CDC proposed two hypotheses related to reactogenicity and adverse events:

1. AVA administered by the IM route results in decreased local reactogenicity compared with SQ administration.
2. Occurrence of adverse events following AVA administration is influenced by selected risk factors.

Study Design

The study is designed as a prospective, randomized, double-blind,[3] placebo-controlled clinical trial to be conducted over a period of 43 months at five sites in the United States. As described in Chapter 4, the study population will consist of 1,560 healthy civilian adult men and women between the ages of 18 and

[3] Unblinded staff will prepare and administer the vaccine or placebo, but CDC staff, the investigators monitoring and analyzing immunogenicity and reactogenicity, and the participants will remain blinded to study group assignment.

61 years. Recruitment efforts will focus on groups for whom AVA vaccination for bioterrorism preparedness has been considered, including emergency first responders, federal responders, and medical practitioners.

Study participants will be randomly assigned to one of six study groups of 260 persons each, in a manner that ensures that at least 20 percent of the members of each study group will be women. One study group will receive eight SQ doses of AVA in accordance with the currently licensed schedule. A placebo group will receive eight injections of sterile saline; half of the group will receive SQ injections and half will receive IM injections. In the four other study groups, participants will receive either four, five, seven, or eight IM doses of AVA. Participants who receive fewer than eight doses of AVA will receive an injection of the saline placebo in place of an omitted dose of AVA.[4] All vaccine doses are to come from AVA Lot FAV063, manufactured by BioPort Corporation as a "post-renovation qualification lot" (CDC, 2002a, p. 61).

Study participants will be actively monitored for adverse events following scheduled injections. Each person will have a total of 22 clinic examinations for assessments of a set of predefined local and systemic adverse events (referred to as solicited adverse events) and of other health-related endpoints (see Box 5-3). In addition, participants will receive 14-day diaries after each of the first two injections and 28-day diaries after each subsequent injection to record adverse events. They will also receive digital thermometers to measure oral temperature at bedtime for the four days following an injection. Clear circular rulers will be given to participants so that they can measure the diameter of any injection-site reactions.

The information from the clinical assessments and diaries will be used to determine the presence or absence of the specified adverse events, the presence or absence of any adverse event rated moderate or severe, and the total number of events. Local and systemic events will be considered separately. The number of days of restricted activity each study participant experiences as a result of adverse events will also be assessed. In addition, the study protocol calls for participants to complete the SF-36 v2 Health Survey (described below) at enrollment and at 12, 18, 30, and 42 months. Over the course of the study, each participant will also have a total of 16 blood samples drawn.

Data will be collected from study participants for analysis of potential risk factors for adverse events. The risk factors to be considered include (but are not limited to) age, sex, body mass index, hormonal status (women only), known allergies, physical activity level, smoking status, perceived general health status, number of previous doses of AVA, pre-injection titers of anti-protective antigen immunoglobulin G and toxin neutralizing antibody, history of adverse events associated with previous doses of AVA or with doses of other vaccines, and study participants' beliefs at the conclusion of the study as to whether they had received doses of the vaccine or the placebo. The analysis will compare men and women in terms of the reactogenicity of the vaccine and the influence of various risk factors on the occurrence of adverse events.

Planned Analyses

The study protocol specifies that the primary reactogenicity analyses will be conducted using the participants who can be evaluated according to protocol and that an intent-to-treat analysis will be used to assess whether deviations from the protocol biased the results.[5] CDC will contract with statistical experts to examine deviations from the protocol in the form of dropouts, noncompliance, and loss to follow-up and to devise appropriate analyses.

The proposed analysis will test for less reactogenicity with IM administration than with SQ administration in the two study groups receiving the full eight doses of AVA. In addition to the overall IM–SQ comparison, IM–SQ comparisons will also be performed separately for men and women. Per-dose and repeated-measures analyses will be performed, and a one-sided test of significance (alpha = 0.025) will be

[4] See Table 4.1 in Chapter 4 for the schedule of injections for each study group.

[5] See Chapter 4 for an explanation of the differences between according-to-protocol and intent-to-treat analyses.

BOX 5-3
Categories of Adverse Events to Be Identified During the Human Clinical Trial

Solicited Adverse Events

Within 28 days of vaccination: fever, fatigue, muscle ache, headache, temperature, axillary adenopathy, warmth, tenderness, itching, pain, arm motion limitation, erythema, induration, nodule, bruise

Serious Adverse Events

Any time during the study: death, life-threatening adverse event, initial inpatient hospitalization or prolongation of hospitalization (including pregnancy), significant or persistent disability/incapacity, congenital anomaly or birth defect, or any important medical event based upon appropriate medical judgment that may jeopardize the participant and may require medical or surgical intervention to prevent one of the other outcomes defined as a serious adverse event.

Other Adverse Events

Any other adverse event that cannot be classified as a solicited adverse event.

SOURCE: CDC, 2002a, pp. 79–80.

used. The occurrence of local and systemic effects will be considered separately, based on a dichotomous measurement of the presence or absence of specified adverse events as detected during clinical examinations or recorded in participants' diaries. The total number of days of restricted activity per participant will also be compared.

Separate analyses will compare all study groups to assess the effect on reactogenicity of a reduction in the number of vaccine doses along with the change in route of administration. Exploratory analyses will test for differences in the severity of adverse events and in perceived general health and well-being (based on responses to the SF-36). Other exploratory analyses will examine the association of various risk factors with the occurrence of adverse events. To test for significant differences between men and women, comparisons will be made within each of the six study groups (two-sided test, alpha = 0.05).

Another exploratory analysis will test whether premenopausal women differ in the occurrence of adverse events depending on their hormonal phase (follicular or luteal) at the time of vaccination. One comparison will be restricted to women receiving SQ doses of AVA. The other comparison will include all eligible women. The study protocol notes that these analyses will focus primarily on women who are not using pharmacologic methods of birth control and that special efforts may be necessary to recruit adequate numbers of women meeting this requirement.

A Data and Safety Monitoring Board will review quarterly progress reports on the study and will assist in the preparation of the interim analysis of the data from the first 7 months of the study. This board will also monitor the occurrence of any serious adverse events or procedural problems that might warrant a recommendation to terminate the study.

Committee Comments

On the whole, the committee found that the study, as described in the protocol, is generally appropriate for comparing the reactogenicity of SQ and IM administration of AVA. The basic analyses related to the association between the route of vaccine administration and the occurrence of adverse events should have, and do seem to have, the highest priority. The plans for monitoring adverse events should produce the most systematic assessment to date of those events that occur with relatively high frequency within the 42-month time frame of the study. It will, of course, be unable to provide insights regarding less frequent, albeit serious, events.

In addition, the use of vaccine from a lot manufactured following the completion of the renovation of the BioPort facilities will provide an opportunity for systematic documentation of the reactogenicity of the newly manufactured vaccine. The availability of such data will help guide the routine monitoring of the vaccine called for by the IOM review of the efficacy and safety of AVA for the Department of Defense (DoD) (IOM, 2002). The committee also commends CDC for assembling a strong and well-balanced Data and Safety Monitoring Board, whose members have substantial experience with studies of the safety and efficacy of vaccines.

Finding: As described in the study protocol, the human clinical trial is generally responsive to the congressional mandate to evaluate the incidence of, risk factors for, and differences between men and women in local and systemic immediate-onset health effects associated with AVA and the effect of the route of vaccine administration on adverse events. The study will also provide a 42-month follow-up period during which to monitor the occurrence of later-onset health effects.[6]

The committee noted one area of concern related to the proposed statistical analyses of reactogenicity. The study protocol specifies that the primary analysis will test the hypothesis that IM administration of AVA results in reduced reactogenicity compared with SQ administration and that a one-sided statistical test of significance will be used. It appears that this approach was chosen to parallel the immunogenicity analysis to establish the "non-inferiority" of antibody response to IM administration compared with the response to SQ administration. However, it may not be justified for the analysis of differences in reactogenicity.

To justify a change to IM administration of AVA, the immunogenicity analysis must show that IM administration of the vaccine results in an antibody response considered at least as good as the response with SQ administration. If IM administration does not perform as well as SQ administration, there will be no basis for changing the current practice of SQ administration and little reason to establish whether the antibody response for IM administration is significantly worse than that for SQ administration. Therefore, one-tailed statistical testing is appropriate.

For reactogenicity, however, the hypothesis being tested is that IM administration of the vaccine is superior to SQ administration (i.e., less reactogenic) rather than not inferior. The proposed use of a one-sided test of statistical significance does not allow for the detection of inferior performance, that is, whether any adverse events occur at significantly higher rates with IM administration of AVA than with SQ administration of the vaccine.

Assuming that the study can provide satisfactory indications that the antibody response with IM administration of the vaccine is at least comparable to that with SQ administration, the decision as to whether to modify the route of administration should also take into account the likely impact on the frequency and severity of recognized adverse events. If IM administration of the vaccine proves to be significantly less reactogenic in terms of all the proposed indicators, use of a one-sided statistical test is sufficiently informative, and the decision to adopt IM administration is straightforward. However, if some indicators were to show that reactogenicity is not reduced with IM administration, it would be important to establish whether IM administration resulted in increased reactogenicity over SQ administration before deciding to change the licensed indications for use of AVA. A two-tailed statistical test is necessary to differentiate both decreased and increased reactogenicity from no difference.

The plans for using one- or two-tailed statistical tests in the analyses of risk factors for reactogenicity are unclear. For these analyses, the committee sees no basis for one-sided tests unless a clearly articulated biological rationale can be provided.

[6] The committee has adopted the terminology used by the Committee to Assess the Safety and Efficacy of the Anthrax Vaccine (IOM, 2002). The phrases "short term" and "long term" were not used to characterize adverse events because of the potential for confusion. Instead, the duration of an adverse event is characterized as acute or chronic; the timing of the onset of an adverse event is characterized as immediate or later.

Recommendation: The analyses of reactogenicity in CDC's human clinical trial of AVA should use two-sided statistical tests.

The likely loss of participants over the course of the study should also be considered. The study protocol notes that sample sizes were calculated to allow for the loss of up to 50 percent of participants. As noted in Chapter 4, the committee urges that CDC and the centers participating in the study ensure that those interested in participating are fully informed about the demands of the study, including the vaccination schedule and the time commitment involved. Also as noted in Chapter 4, the committee urges continued consultation with experts in the analysis of data from clinical trials with significant loss to follow-up or noncompliance, as well as consultation with FDA, to ensure appropriate analysis of the data from the clinical trial.

The most important analyses are those necessary to establish the route of vaccine administration and the number of vaccine doses that produce immunogenicity at a level at least comparable to that of the current regimen while minimizing reactogenicity. The study appears adequately powered for these analyses. However, the committee is concerned that the size of the study population will not provide adequate statistical power for some proposed analyses. As noted in the committee's interim report (IOM, 2001), it may not be possible to analyze risk factors for adverse events among men and women separately. Similarly, analyses of other demographic factors that are of interest, such as age and race, may be hampered by lack of statistical power. It may also prove challenging to perform the planned analysis of the possible association of hormonal phase with the occurrence of adverse events because of the need to recruit adequate numbers of premenopausal women who are not using pharmacologic methods of birth control.

The committee also observes that the expectation reflected in the protocol that the inclusion of placebo groups will permit the evaluation of rates of rare adverse events is unrealistic because of the difficulty of detecting truly rare events (e.g., incidence less than 100 per 100,000) in a study population of this size. Other approaches, such as the analysis of data from large observational data sets like those of the Defense Medical Surveillance System (DMSS), appear far better for studying the incidence of rare adverse events.

A final observation concerns the planned use of the SF-36 to assess whether vaccination is associated with differences in perceived general health and well-being. As in its interim report, the committee endorses the general goal of assessing the health status of vaccinees. It is essential, however, to recognize the limitations of the SF-36 for this purpose in the context of the human clinical trial.

The SF-36 is a well-studied and extensively validated instrument for the self-assessment of health status, principally for producing a generic measure of the burden of disease (Ware et al., 1993). The SF-36 produces scores on eight broad aspects of physical and emotional functioning and well-being[7] and two summary scores on physical and mental health. But because the SF-36 is designed primarily to detect substantial differences in health status as a result of disease or injury, it is unlikely to be sensitive enough by itself to make meaningful distinctions among small changes in a generally healthy population, such as the participants in the human clinical trial.

The committee encourages CDC to supplement the SF-36 with other instruments, such as a symptom checklist or other validated assessment tools specifically related to possible adverse events or to specific complaints (e.g., fatigue, cognitive impairment, or reduced productivity). The additional information would facilitate interpretation of the SF-36 results through comparisons of persons with and without certain symptoms or would permit direct assessments of the impact of specific adverse events. The committee's reservations about the proposed use of the SF-36 are also discussed later in the chapter in conjunction with the review of the studies to be based in the Vaccine Healthcare Center (VHC) Network.

[7] The eight health concepts measured by the SF-36 are limitations in physical functioning, limitations in usual role (e.g., worker, student, etc.) because of physical health problems, bodily pain, general health, vitality, limitations in social functioning because of physical or emotional problems, limitations in usual role because of emotional problems, and mental health.

FOLLOW-UP STUDY OF TEXTILE MILL WORKERS VACCINATED AGAINST ANTHRAX

CDC has proposed to study the possible chronic or later-onset health effects of AVA vaccination by examining the mortality experience and functional status of textile mill workers who received doses of AVA 10 or more years ago. A draft study protocol was submitted to the committee for review (see CDC, 2002b,g).

Study Design

A retrospective cohort study has been proposed. The study population will be drawn from former workers at one textile mill that processed goat hair from the mid-1960s through the mid-1990s. The mill required vaccination against anthrax for its entire workforce, which averaged 800 to 1,000 workers at any given time. Immunization records were maintained by a company-employed nurse but had not been located at the time the study proposal was provided to the committee.

CDC is working with the Social Security Administration (SSA) to identify former employees of the mill. As of January 2002, CDC had received information on 3,172 persons employed at the mill or by its parent company during the period 1978–1996; of this group 337 may have worked at another site, making them ineligible for the study. Deceased workers will be identified using the National Death Index. CDC will obtain contact information for surviving workers through a process developed for and successfully used in studies by the National Institute of Occupational Safety and Health (NIOSH).

CDC estimates that 2,605 of the 3,172 workers identified from the SSA records are still alive. Assumptions that 15 percent of the survivors will be lost to follow-up and that 70 percent of those located will participate suggest a vaccinated study cohort of 1,550 persons. Preliminary calculations indicate that for outcomes with a prevalence of 1.0 percent this sample size will provide a power of 97 percent to detect a fivefold increase in risk and power of 57 percent to detect a twofold increase in risk. For outcomes with a prevalence of 0.5 percent, the power to detect a fivefold or a twofold increase in risk is estimated to be 74 percent and 28 percent, respectively.

Two comparison groups of unvaccinated persons are planned. One group will be drawn from the community in which the goat hair mill was located. Participants will be recruited from the census tracts in which vaccinated workers now live and frequency-matched in terms of age, sex, and race. An occupational comparison group will consist of persons who worked in other kinds of textile processing mills in the same region of the country as the goat hair mill and during the same time period as the members of the vaccinated study group. Participants will be selected by frequency matching on age, sex, and race.

Information will be collected on participants' demographic and socioeconomic characteristics and on various health-related risk factors, including occupational history, personal and family medical history, use of medical care, and history of disability claims. The questionnaires and interview forms used to collect this information will, to the extent possible, be based on various national survey instruments (e.g., National Health Interview Survey, the Longitudinal Survey of Aging, and the Current Population Survey).

Health outcomes will be assessed using measures that can provide objective evidence of pathology that could be examined further in subsequent studies. For this initial study, the measures, which are not necessarily linked to specific clinical endpoints, include excess mortality (overall and cause-specific), excess morbidity, and measures of current functioning.

For the goat hair mill workers who have died, CDC will ascertain their dates of death and underlying and contributory causes of death (coded according to the ICD-9). CDC will also obtain the death certificates for these workers. Medical conditions for which data from the self-reported medical histories of the surviving goat hair mill workers show a statistically significant excess compared with the control groups will be verified by a review of participants' medical records.

The assessment of current functioning will include the following four components, measured using the specified tools:

1. Health status and health-related quality of life (HRQoL), measured using the SF-36 and the Health Utilities Index (versions 2 and 3)
2. Energy or activity level (no tools specified)
3. Cognitive function, measured using the Halstead-Reitan Neuropsychological Test Battery (selected subtests), the Wechsler Memory Scale (Third Edition), and continuous performance tests and measures of attention
4. Immunologic function, measured using a complete blood count with differential, lymphocyte subsets, immunoglobulin levels, complement levels, T-cell proliferation assays, skin tests for anergy, and thyroid hormone levels.

The criteria considered by CDC in selecting these measurement tools included the availability of population-based norms, a demonstrated usefulness in clinical and research studies, and logistically feasible and tolerable requirements for administration. To the extent possible, all participants will complete all assessments.

An extramural advisory panel will be convened before the study begins to advise CDC on the study design, the selection of tests of current functioning, and criteria for the interpretation of test results. The same panel (or a similar one) will reconvene periodically to provide advice during the collection and analysis of data.

Planned Analyses

The analysis of the mortality experience of the vaccinated population will be based on the calculation of standardized mortality ratios (SMRs) for overall and cause-specific mortality. The SMRs will compare observed mortality with that expected based on death rates for the United States as a whole, for the state in which the goat hair mill was located, and for the occupational comparison group. Computer programs developed by NIOSH for life table analysis and Poisson regression analyses will be used to account for person-years at risk. The study protocol notes that if there is an indication of excess deaths among the vaccinated workers, it will be necessary to allow for possible survivor bias in the analysis and interpretation of other data.

The assessment of health-related life experiences and current functioning among vaccinated workers and the comparison groups will make use of descriptive statistics (e.g., means, frequency distributions) to characterize study participants. Various parametric and nonparametric analytical techniques will be used to compare health outcomes between the vaccinated population and the unvaccinated comparison groups. Risk associated with exposure to AVA will be measured using multivariate techniques (e.g., linear or logistic regression, Cox proportional hazards models). Matching criteria will be included as covariates in all statistical models.

Committee Comments

This study is intended to address the questions of whether receipt of AVA is associated with chronic health impairments or with adverse health effects that become apparent only after several years (later-onset health effects). The committee agrees that these questions deserve attention. Vaccinated workers in textile mills that processed goat hair are clearly an appropriate population to consider studying. They represent one of the primary target populations for vaccination during the 1960s, 1970s, and 1980s. Some of the textile mill workers from the proposed study population may have begun receiving AVA on a regular basis from the time it became available in the 1960s, offering the possibility of as much as 30 years of follow-up. In addition, the plans to include two comparison groups—a community group and an occupational group—reflect an awareness of some of the challenges of studying occupational health risks.

Nevertheless, the committee has serious reservations about the proposed study. The most important concern is the risk of a selection bias: there is no truly comparable control group available. The use of an

occupational comparison group is an appropriate effort to compensate for the "healthy worker effect" that is often found in comparisons between working populations and community controls. But it may be impossible to establish the true comparability of the workplace exposures in the textile mills that processed goat hair with those in other types of textile mills in the region. As such, any finding that emerges, whether positive or negative, has too high a risk of being spurious, due to making comparisons between groups that are not equivalent in ways other than their exposure to AVA.

Another important fact is that the study is too small and therefore lacks sufficient statistical power for a meaningful assessment of differences in mortality and disease risks and in other health outcomes between the vaccinated population and the comparison groups. The estimates of statistical power in the study proposal use 0.5 percent (500 cases per 100,000) as a minimum estimate of the prevalence of a hypothetical outcome of interest. The committee notes that cohort studies usually rely on measures of incidence rather than prevalence. In basing its calculations on prevalence, CDC may have underestimated the difficulty of detecting events of interest in a cohort of the size anticipated for this study. Regardless, the events of interest regarding AVA are much less common than the rates evaluated in CDC's sample size calculations. An analysis of DMSS data, for example, found that postvaccination hospitalization rates among military personnel who received AVA were 92.5 per 100,000 for all neoplasms (ICD-9-CM codes 140–239); 32.5 per 100,000 for all endocrine, nutritional, metabolic, and immunity disorders (ICD-9-CM codes 240–279), and 67.2 per 100,000 for all diseases of the nervous system (ICD-9-CM codes 320–389) (AMSA, 2001). Within these summary categories, hospitalizations for individual diseases—which are more plausibly associated with vaccination—were much rarer. While these rates are based on a shorter period of observation than would be the case in the proposed study, they illustrate the incidence of medically significant events observed in a large population of vaccinees.

Furthermore, the committee questions the validity of the assumptions used to project the likely size of the study population. The expectation that only 15 percent of the survivors will be lost to follow-up and that 70 percent of those contacted will participate seems overly optimistic. Greater loss to follow-up or lower participation rates will only increase the probability of a spurious association (or a spurious lack of an association) as it is quite likely that the few outcomes of interest would be missed. Such losses will also exacerbate the problem of low statistical power.

In addition, the study also poses the statistical risk of generating spurious associations, either positive or negative, between vaccination with AVA and various health outcome measures because of the large number of proposed outcome measures and analyses described in the study protocol. It is reasonable to expect some statistically significant associations to arise by chance alone.

Unidentified confounding factors might also serve to obscure true differences in health outcomes between the vaccinated and unvaccinated populations. The study might produce incorrect positive findings due to this uncontrolled confounding or selection bias, and it could miss true positive findings, even in the unlikely event that the signal was strong enough to be detected in a study this small.

Another serious concern is the potential for misclassification bias. The validity of the analysis would be weakened if workers who were assumed to be vaccinated were not or if the number of doses they had received was not accurately recorded. The study protocol noted that the immunization records for workers at the goat hair mill had not yet been located. Once again, this bias could result in a masking of true findings.

Given the limitations of the proposed study, the committee is concerned that participants face inappropriate risks. The study process will be intrusive, and asking participants about their health status and medical histories could be construed as meaning that health problems are anticipated. In addition, the false signals that random error or bias in the data may generate could result in unnecessary anxiety or medical tests and interventions.

Instead, the committee urges consideration of alternative approaches for investigating whether receipt of AVA is associated with chronic or later-onset health effects. In particular, the committee encourages the development of plans that will permit follow-up of military personnel who received the vaccine. This

might be done through DMSS or the Millennium Cohort Study, which will follow up to 140,000 military personnel during and after their military service. The use of data from DMSS and other sources is discussed in more detail later in this chapter in conjunction with other study proposals.

Finding: The committee concludes that the preliminary exploration of a study of possible chronic or later-onset adverse events related to anthrax vaccination among goat-hair textile mill workers, with community and occupational comparison cohorts, was appropriate. That effort, however, has produced sufficient information to indicate that the study (1) poses the risk of generating spurious associations or masking real associations, in part because of the difficulty of identifying suitable comparison groups, and (2) would not have sufficient statistical power to detect conditions of interest. Furthermore, with these limitations, conducting the study poses the risk of generating unwarranted health concerns among the participants.

Recommendation: CDC should not continue work on the proposed follow-up study of textile mill workers who received AVA.

STUDIES BASED IN THE VACCINE HEALTHCARE CENTER NETWORK

The committee reviewed draft protocols for three studies to be conducted through the VHC Network (CDC, 2002c,h,i). The VHC Network is a collaboration between DoD and CDC to address issues of safety and acceptability of all types of vaccines administered within the military health care system (CDC, 2002h). The first VHC was established at Walter Reed Army Medical Center in Washington, D.C., in September 2001. Plans call for a total of 10 to 12 VHCs to be opened over the next 5 years.

The goals for the network are to serve as a platform for studies of vaccine-related adverse health events and to enhance the immunization-related health care of military personnel. DoD is to focus on the clinical management of vaccination services and the care and follow-up of service personnel who experience vaccine-associated adverse events. CDC is to focus on observational research on vaccine safety, pilot tests of vaccine safety and acceptability activities and interventions, and assessments of the impact of the VHC Network on vaccine safety and acceptability. Concerns related to AVA will be the initial focus of these activities, but the VHC Network is expected to address issues related to other vaccines, as well.

The three study proposals reviewed by the committee use an observational study design in a military population to replicate certain components of the human clinical trial (discussed above). Specifically, these studies are to examine (1) the effects of the route of AVA administration on adverse events that occur soon after vaccination, (2) the effect of AVA on HRQoL, and (3) the effect of hormonal phase on the occurrence of adverse events in women receiving AVA. Each study proposal is discussed in more detail below. The proposal notes that these studies will complement the human clinical trial by overcoming some of its limitations, in particular, the trial's low statistical power to test some risk-factor associations and the need to wait until the completion of the study (43 months) to perform some of the analyses.

The drafts of the study proposals reviewed by the committee specify that participants are to be recruited from random samples of military personnel (active duty and reserves) scheduled to receive AVA vaccinations. Vaccination of personnel scheduled for deployment to high-risk areas has the highest priority. Study subjects will be permitted to participate in more than one of the proposed studies, but the initiation of the studies and the continued recruitment of subjects will depend on the pace at which service members are vaccinated under DoD's new anthrax vaccination policy, announced in June 2002 (Wolfowitz, 2002). In addition, two of the proposed studies plan for cohorts that receive IM doses of AVA or that receive a new recombinant anthrax vaccine. The proposal notes that the inclusion of these cohorts will depend on the Food and Drug Administration's (FDA) licensure of AVA for IM administration and of a new anthrax vaccine product when it becomes available.

Study participants will not necessarily be vaccinated at a VHC location, and plans are being developed for VHC oversight of AVA vaccinations administered at other sites. Military medical staff will be

trained by CDC staff to conduct the studies and collect data from study participants. VHC nurses will be trained by CDC staff and will monitor the quality of the study procedures.

The draft protocol for these studies specifies that the Anthrax Vaccine Expert Committee, an independent civilian advisory panel convened in 1998 by the Department of Health and Human Services, will assess all adverse events reported by study participants to make a determination as to whether the event is causally related to receipt of the vaccine. Events will be classified into one of the following causality categories: definite, probable, possible, unlikely, not related, or unclassifiable.

CDC indicates that an advisory panel is to be formed to review the study protocol and advise on the study design. Members of the advisory panel are to have expertise in anthrax, behavioral psychology, reproductive physiology, and biostatistics. The panel is to include representatives from the VHC network, DoD, and military groups who can comment on the feasibility and logistics of these studies.

The committee did not review or evaluate the clinical, educational, or quality improvement programs to be undertaken by the VHCs, confining its critique to the three research proposals submitted by CDC.

Effects of Change of Route of Administration on Local Adverse Events Following AVA Vaccination

As noted, this study mirrors key elements of the human clinical trial. Two principal hypotheses have been specified (CDC, 2002c):

1. Service personnel receiving AVA administered by the IM route will have fewer adverse events than those receiving AVA by the SQ route.
2. The occurrence of adverse events following the administration of AVA is influenced by selected risk factors, including gender.

Study Design

The VCH-based study of the relationship between route of AVA administration and the occurrence of adverse events is planned as a prospective observational study with three cohorts. The first cohort will receive AVA according to the currently licensed regimen of SQ administration of the vaccine. For each of the first three vaccine doses, medical personnel will examine study subjects for local reactions at 15 to 25 minutes after vaccination and at a clinic visit 1 to 3 days after vaccination. Subjects will also receive diaries to record other adverse events. If IM administration of AVA is approved, the second cohort will receive the vaccine according to the licensed regimen for IM administration. The members of this cohort will be monitored in the same manner as those in the first cohort. A third cohort will be recruited if a new anthrax vaccine becomes available for use by the military.

At the time the study proposal was submitted to the committee, sample size calculations had not been made for these cohorts. CDC was awaiting information from DoD on the sampling frame. The study protocol notes that recruiting subjects for each cohort at different points in time introduces the possibility that the factors influencing reporting behaviors with regard to adverse events may differ among the cohorts.

As in the human clinical trial, postvaccination assessments will determine the presence or absence of specified ("solicited") adverse events, the presence or absence of any adverse event rated moderate or severe, and the total number of events. Local and systemic events will be assessed separately. The number of days that participants are affected by adverse events and the number of days that participants experience restricted activity as a result of adverse events will also be assessed. The data to be collected for an analysis of risk factors, other than sex and other "demographics," are not described. Missing data will be assumed to be missing at random, unless available data suggest otherwise. If necessary, methods of data imputation will be explored.

Planned Analyses

The primary focus of the data analyses will be to assess the differences between men and women and between SQ and IM administration of AVA in the nature and frequency of adverse events. The study protocol specifies that the risk-factor analyses will be conducted before and independently of the analyses related to the route of administration. Differences between SQ and IM administration are generally to be assessed with one-sided tests of significance (alpha = 0.05).

Four sets of per-dose analyses are planned. A one-tailed Fisher's exact test will be used to test the null hypothesis of no difference in local or systemic reactogenicity between IM and SQ administration of the vaccine. Fisher's exact test will also be used to assess differences in the number of adverse events per person, the number of days of restricted activity related to adverse events per person, and the duration and size of local adverse events. The extended Mantel-Haenszel mean score statistic may be used for the analysis of the numbers of adverse events, and the duration of adverse events will be analyzed as a continuous variable using the Mann-Whitney test. To account for the anticipated inclusion of multiple observations of study subjects who receive more than one dose of AVA over the course of the study, repeated measures analyses will also be performed for differences by route of vaccine administration in the occurrence and number of adverse events and in the duration of adverse events and restricted activity.

Committee Comments

In general, the committee agrees with the appropriateness of conducting, as a complement to the human clinical trial, a cohort study to assess the effect of a change from SQ to IM administration of AVA on the occurrence of adverse events. The study would be comparable to postmarketing studies that are routinely conducted following the introduction of new pharmaceutical products. Such studies are valuable for two purposes: (1) confirming in a general population the rates of adverse events observed in clinical trial participants, and (2) detecting, through longer observation of a much larger population, medically significant but rare adverse events that were not observed in a clinical trial.

For the first of these purposes—to confirm rates of common adverse events that occur soon after administration of AVA—a cohort study should use intensive active surveillance to monitor a study population similar in size to that of the clinical trial. The committee considers it feasible to obtain this type of useful postmarketing data through CDC's proposal for a VHC-based cohort study. The plan to ascertain adverse events through a combination of clinical examinations and diaries completed by study participants would provide an appropriate level of surveillance. As noted above, however, the size of the study population had not been determined at the time the proposal was submitted for review.

Finding: Postmarketing-type cohort studies of anthrax vaccine use are appropriate for two purposes:

1. **to confirm in a population not participating in a clinical trial the findings from the clinical trial regarding rates of adverse events commonly associated with receipt of AVA, differences between subcutaneous and intramuscular administration in rates of adverse events, and risk factors for adverse events and**
2. **to detect rare but medically significant adverse events that will be found only by observing a larger population over a longer period of time than is possible in the human clinical trial.**

Recommendation: A VHC-based study to verify reaction rates to AVA and the validity of self-reported data observed in the clinical trial should provide for intensive active surveillance of relatively small cohorts, similar in size to the study groups in the human clinical trial.

As the committee noted in commenting on the proposal for the human clinical trial, the plan to use one-sided statistical tests to assess differences in reactogenicity between SQ and IM administration of

AVA is inappropriate without a clearly specified biological justification. Two-sided tests of significance (alpha = 0.05) should generally be used. Any biologically justified one-sided tests should use a significance level of 0.025.

The committee also notes that no date has been specified for the implementation of this study. The opportunity to make the proposed comparison of adverse events following SQ versus IM administration of AVA will depend on when the study begins. It is anticipated that an interim analysis of the data from the human clinical trial, which is scheduled to be available in the fourth quarter of 2003, will result in FDA approval of a change in the labeled route of administration of AVA from SQ to IM. Because DoD will administer AVA in accordance with the label, participants for an SQ cohort must be recruited before the expected labeling change occurs.

In addition, CDC reported plans to assume that missing data are missing at random. It will be important during the course of the study to collect the information necessary to test that assumption. The study should also include procedures aimed at minimizing missing data. CDC should consult with statistical experts to ensure that the available data are analyzed appropriately.

Finding: Because of the anticipated labeling change that will specify intramuscular administration of AVA, a VHC-based study of adverse events must be initiated promptly if it is to follow a cohort of military personnel who receive AVA subcutaneously.

The second type of postmarketing study—of less common but medically significant adverse events—would require a different approach from that described in the CDC proposal. To conduct such a study, it would be necessary to monitor a large population (probably 10,000 or more persons), but in a less intensive manner than that described in the study proposal. The monitoring process should emphasize the capture of information on health outcomes that require clinical care. This type of study would also require a longer period of surveillance than has been proposed, and plans would be needed for appropriate analyses to assess the likelihood that receipt of AVA is causally related to any adverse outcomes detected.

Such a study would also require a control group that does not receive the anthrax vaccine and whose members are comparable in initial health status to the study participants who are vaccinated. There are, however, significant challenges in assembling a suitable control group. The factors that affect the likelihood of vaccination may also be related to health status. In the past, the military personnel most likely to receive AVA have been those deployed to areas considered to present a high risk of exposure to bioweapons (e.g., South Korea, Southwest Asia). Therefore, personnel who were vaccinated were also likely to be healthier on average than those who were not vaccinated because health problems may disqualify an individual from deployment. Data from DMSS evaluated at the request of another IOM committee indicated a strong "healthy deployer effect" for personnel who received AVA (IOM, 2002). This relationship between health status and vaccination is likely to continue, given the DoD announcement in June 2002 that resumption of the Anthrax Vaccine Immunization Program (AVIP) would be limited to military personnel assigned to or deployed for more than 15 days in higher threat areas and "whose performance is essential for certain mission critical capabilities" (Wolfowitz, 2002, p. 1).

Finding: A large cohort study intended to detect the occurrence of less common, medically significant adverse events following receipt of AVA would require the inclusion of a control group that has not received AVA and that is comparable in initial health status to the vaccinated cohorts. Because vaccination is related to deployment and deployment is related to health status, it would be challenging to assemble a suitable control group.

Previous analyses (see IOM, 2002), however, provide no basis for suspecting that AVA is associated with serious health problems. Thus, this committee questions the need for a special study of this sort. Furthermore, the committee is not persuaded that the VHC Network is the appropriate base for the sort of extended surveillance of a large population that would be needed for this kind of study when other resources are available for obtaining health data on military personnel. As emphasized in the IOM (2002) report to DoD on the safety and efficacy of the anthrax vaccine, the data from DMSS on inpatient and

outpatient care are a uniquely valuable resource for monitoring the health of military personnel who receive AVA or other vaccines. Data from the Millennium Cohort Study or from the health care system of the Department of Veterans Affairs (VA) might provide other means through which to assess whether rare adverse events are associated with receipt of AVA. The use of data from DMSS is discussed further in connection with the study proposals on enhanced signal detection and hypothesis testing.

Effect of AVA Vaccination on Health-Related Quality of Life

This study is based on using the SF-36 version 2 (v2) Health Survey (Ware et al., 1993), described above, to obtain data on the HRQoL of military personnel scheduled for deployment to areas considered to have a high risk of exposure to anthrax bioweapons.

The study is intended to test the following hypotheses (CDC, 2002i, p. 9):

1. AVA administered SQ has an effect that is no different from that of other predeployment non-AVA vaccines on the perceived general health and well-being of service personnel.
2. AVA administered SQ has an effect that is no different from that of AVA administered IM on the perceived general health and well-being of service personnel.
3. AVA administered IM has an effect that is no different from that of a new/recombinant anthrax vaccine on the perceived general health and well-being of service personnel.

Study Design

Plans for this prospective observational study call for four cohorts of 322 persons each. The first cohort will not receive AVA. The proposal indicated that this group would be recruited at the beginning of the study when it was anticipated that a limited supply of AVA would preclude administering the vaccine to some or all personnel to be deployed to high-risk areas.[8] As proposed, these study participants will complete the SF-36 before receiving their other predeployment vaccinations and at 6-month intervals for 2 years, or until AVA vaccination resumes. The second cohort will be recruited when regular predeployment vaccination with AVA resumes. For this cohort, the vaccine will be administered subcutaneously. The members of this group will complete the SF-36 before receiving an initial dose of AVA and at 6-month intervals for a 2-year period. (The committee assumes these study participants will also receive other routine predeployment vaccinations.) The third cohort will be recruited only after the anticipated change to IM administration of AVA is approved. As with the second cohort, the members of the third group will complete the SF-36 before receiving the first dose of AVA and at 6-month intervals for a 2-year period. The fourth cohort will be recruited only if a new anthrax vaccine is approved and available for DoD use. Each participant will complete the SF-36 up to five times over the course of the study.

Planned Analyses

The analysis will assess whether the cohorts differ significantly at the end of the study period in terms of the change from the baseline in each of the two SF-36 summary measures. The change in the summary measures will be treated as a continuous variable, and the analysis will use repeated-measures procedures. Several different covariance structures will be tested, and Tukey's Studentized Range Test will be used for pairwise comparisons of least square means. Because the cohorts will be recruited at different times, their baseline SF-36 measures will be compared. If significant differences are found, the baseline summary scores will be included as covariates.

[8] DoD's decision to resume administration of AVA to some military personnel scheduled for deployment was announced in June 2002 (Wolfowitz, 2002), four months after CDC's proposal for this study had been submitted to the committee for review.

Committee Comments

Given the concerns that have been expressed by some about the adverse impact on overall health and well-being of vaccination with AVA, the committee agrees in general with the concept of a study to assess differences in health-related quality of life associated with receipt of AVA. There are, however, several concerns about the specific study that has been proposed. First, as noted in the comments on the related component of the human clinical trial, the SF-36 generally performs poorly in detecting meaningful differences in the health status of generally healthy populations. Because the proposed study participants will be scheduled for military deployment, they can be expected to be among the healthiest members of the military population.

Second, the fact that the study participants are to be recruited from among military personnel scheduled for deployment raises a concern about the feasibility of plans to readminister the SF-36 at 6-month intervals over a 2-year period. The study proposal does not address the procedures that will be used to locate study participants or to administer the SF-36 once they are deployed.

Third, the committee is concerned that it will be impossible to validly associate any observed differences in HRQoL with receipt of AVA because the SF-36 results will be confounded by the study participants' exposure to other vaccines and medications administered prophylactically in preparation for deployment, as well as by the potentially substantial effects of a variety of factors resulting from deployment itself. Furthermore, the effects of deployment might vary depending on the deployment duty station (e.g., South Korea versus Southwest Asia). Even with a control group that is deployed but has not received AVA, an adverse impact on health status specifically associated with receipt of AVA would have to be substantial and widespread for differences between groups or changes over time to be detectable and distinguishable from the effect of other confounding factors.

On the basis of these concerns, the committee concluded that the proposed study is unlikely to accomplish its intended purpose.

Finding: The SF-36 is designed to detect large changes in health status. It is not suitable for distinguishing differences in health-related quality of life among basically healthy people such as the military personnel who will receive AVA. Furthermore, in the proposed study population, the confounding effects of exposure to other vaccines and particularly of the experience of deployment are likely to make it difficult to discern any unique effect associated with the receipt of AVA.

Recommendation: CDC should not conduct the proposed VHC-based study of the effect of AVA vaccination on health-related quality of life.

Effect of Hormonal Phase in the Female Population on the Occurrence of Adverse Events Following Immunization with AVA

Menstrual cycle phases and levels of progesterone are considered possible risk factors for adverse events in women following vaccination with AVA. CDC reports in the study proposal that oral contraceptives are prescribed for approximately 80 percent of women in the military, and the effect of these contraceptives on hormone levels must also be taken into account. The study is intended to test the following hypotheses:

1. The occurrence of local adverse events in the 3-day period following vaccination with AVA for women in the luteal phase of the menstrual cycle differs from the occurrence of local adverse events for women in the follicular phase of the cycle.
2. Common pharmacologic birth control methods have an indirect effect on the occurrence of adverse events in women following vaccination with AVA.

Study Design

CDC proposes a prospective observational study. The study population will be recruited from a random sample of premenopausal military women scheduled to receive their first dose of AVA. The sample size will be determined once a sampling frame is provided by DoD. Participants will be asked to provide a blood sample (1 ml of sera) and a pregnancy test before each of their first three doses of AVA. The blood samples will be analyzed at a commercial laboratory to determine the serum progesterone concentrations. Study participants' hormonal phase (luteal or follicular) will be determined on the basis of progesterone levels. If a participant's progesterone level is indeterminate, the starting date of her last menstrual period will be used to help classify the participant's hormonal phase.

Study participants will be given a diary at the time of each vaccination and asked to record all adverse events occurring during the following 3 days. The diaries will also be used to record the use of medications, including prescription contraceptives. Demographic information, such as age and body mass index, will be obtained for each participant.

The draft study protocol notes that for this study, it will be necessary to ensure that a trained phlebotomist is available at the sites where AVA vaccinations will be given.

Planned Analyses

Analyses for this study will first be conducted for women who are not using pharmacologic methods of birth control. They will be repeated for all women in the study, with contraceptive use included as a binary covariate.

The analysis of the effect of hormonal phase on the occurrence of adverse events will use a dichotomous dependent variable, defined as the presence or absence of individual local adverse events. A repeated-measures analysis will be used, with the logit model and a binomial distribution. Additional covariates will be evaluated for inclusion in the model. Progesterone concentration will be analyzed as a continuous dependent variable using a mixed model methodology and repeated measures procedures. Several covariance structures will be evaluated.

Committee Comments

As with the other VHC-based studies, the committee agrees that it is reasonable to plan an observational cohort study as a complement to the related analysis of the association of hormonal status with adverse events that is included in the human clinical trial. However, the committee received limited information on the plans for this study and is concerned that the complexity of the subject will pose serious challenges because of the potential difficulty in identifying adequate numbers of suitable participants and the large number of variables that should be included in the analysis.

In determining the number of participants for each cohort, adequate allowance must be made for the apparently widespread use of prescription contraceptives by women in the military. These contraceptives will affect the physiologic indicators of hormonal phase, and different contraceptives can be expected to have different effects on those indicators. Therefore, accurately determining whether study participants are using prescription contraceptives and which contraceptives they are using will be essential for valid analysis. In addition, it will be important for the analysis to take into account various other factors that could confound the relationship between hormonal phase and adverse events. Some of these other factors include age, race, and parity.

The draft protocol indicated that the size of the study population had not yet been determined. The committee concluded that the sample sizes needed to study these issues will probably be quite large.

Finding: The VHC-based study of the effect of women's hormonal phase on the occurrence of adverse events following receipt of AVA would address a complex subject with many potentially confounding factors (e.g., age, race, parity).

Recommendation: As currently described, the VHC-based study of the relationship between women's hormonal phase and the occurrence of adverse events following receipt of AVA should have a low priority in the CDC research program.

Guidance for VHC-Based Research Activities

Given the complexities evident in the three draft proposals for VHC-based research studies, the committee is persuaded that regular consultation with a standing panel of outside scientific experts will be important for the success of VHC-based research activities related not only to the anthrax vaccine but also to any other vaccine. This group should be able to advise on matters ranging from study design to data analysis. In particular, biostatistical expertise in propensity analysis will be important because the factors that affect the likelihood of vaccination may also be related to health status, as they have been with AVA. Other areas of expertise that may be valuable include health care outcomes assessment, pharmacoepidemiology for guidance on postmarketing surveillance, and possibly clinical epidemiology of medically unexplained symptoms.

The committee is aware that CDC described plans for an advisory panel that will include members from DoD and the military services who can provide valuable advice on the feasibility and logistics of proposed studies. However, it was unclear from the information available to the committee whether the advisory panel was to include members from academia and the private sector and whether it would be a standing group consulted on a regular basis for all VHC research activities.

Recommendation: An external scientific advisory group should be constituted to provide guidance to CDC and DoD on all research undertaken through the VHC network. Given the draft study proposals reviewed by the committee, the advisory group should include, among others, experts in biostatistics (propensity analysis), health care outcomes assessment, pharmacoepidemiology (postmarketing surveillance), and clinical epidemiology (medically unexplained symptoms).

ENHANCED SIGNAL DETECTION AND HYPOTHESIS TESTING FOR ADVERSE EVENTS FOLLOWING ANTHRAX VACCINATION

CDC provided the committee with information on plans to use data from the Vaccine Adverse Event Reporting System (VAERS) and DMSS to investigate adverse events that might be associated with receipt of AVA (CDC, 2002j,k). These investigations will include efforts to detect signals suggesting a possible association between receipt of AVA and an adverse event and efforts to test whether that association might be causal. CDC specified the following objectives:

1. Enhance the capacity to identify adverse events signals from VAERS, the Vaccine Safety Datalink (VSD), and DMSS.
2. Evaluate the association of adverse health events with anthrax vaccine using VAERS and DMSS data.

The committee refers to activities related to the first objective as hypothesis generation, and those related to the second objective as hypothesis testing.

VAERS is the nation's principal system for collecting spontaneous reports of adverse events following the use of any vaccine licensed in the United States. It is jointly administered by CDC and FDA. Anyone can submit a report to VAERS, including vaccine recipients or their family members, and more than one report can be submitted about the same adverse event. Reporting is encouraged for any clinically significant event following vaccination, and health care providers are required to report certain specified events (VAERS, 2001). Limitations of VAERS include duplicate reporting and underreporting of an unknown extent that can vary over time and among various kinds of adverse events, as well as incomplete

and sometimes inaccurate information in submitted reports. In addition, VAERS lacks data on event rates in the unvaccinated population and on the number of vaccine doses administered.

DMSS is a system of DoD-wide databases of health-related information for military personnel on active duty. Data are submitted by the individual armed services, and the system is coordinated by the Army Medical Surveillance Activity (AMSA). The databases include records on inpatient care in military medical facilities since 1990 and records on ambulatory care in military facilities since 1996. Records are also available for all military services on AVA immunizations administered since 1998. Because DMSS captures only events that require ambulatory or inpatient medical care or result in the loss of time from duty, it lacks information on mild adverse events. It also lacks information on care received by military personnel from civilian hospitals or physicians and care that they receive once they leave active duty.

AMSA routinely screens DMSS data for signals of adverse events following receipt of AVA but has lacked the resources to conduct studies to investigate associations that may be identified. To be able to conduct such analyses of DMSS data, CDC is establishing a formal agreement with AMSA for the creation of an Analytic Unit that will be based at AMSA. FDA and the Anthrax Vaccine Immunization Program Agency in DoD will collaborate with CDC and AMSA. Plans call for the Analytic Unit to be operational by August 1, 2002. The initial 3-year agreement is renewable. As presented to the committee, the Memorandum of Understanding establishing the collaboration between CDC and AMSA specifies that CDC will cover costs of up to $500,000 for the first fiscal year and up to $225,000 in each subsequent year.

Hypothesis Generation

Planned Activities

The hypothesis-generating activities described by CDC are to focus on the application of automated exploratory statistical tools and processes, including those referred to as data mining, to the VAERS and DMSS databases to identify groups of adverse events that might be associated with receipt of AVA. Data mining is described as a class of techniques that allow rapid extraction of information from large data sets with many variables. CDC proposed the following specific approaches:

- *Bayesian analysis of VAERS reports* Techniques and software tools that can be used to identify and rank associations among multiple vaccines or multiple adverse events are being developed by AT&T under contract to FDA and CDC. The initial product was a methodology referred to as the multi-item gamma-Poisson shrinkage estimator (MGPS). Software that is easier to use is being developed, and the analytical procedures are being evaluated through sensitivity and specificity estimation.
- *Bayesian analysis of DMSS reports* The methodology developed for use with VAERS data is being adapted for use with DMSS data. Changes in the analytic procedures are necessary to account for the differences between a spontaneous reporting system (VAERS) and longitudinal administrative databases (DMSS).
- *Association analysis of VAERS reports* This approach, also referred to as market basket analysis, is used with VAERS data to search for combinations of one or more vaccines with one or more adverse events. Demographic characteristics can also be incorporated in the analysis. The results are expressed in terms of association rules, and a measure of the strength of the association is produced. The analysis requires relatively little computing time and can be repeated at regular intervals (e.g., quarterly, yearly) to assess changes.
- *Association analysis of DMSS reports* As with VAERS data, the analysis of DMSS data is expected to identify associations within a large, complex data set. The nature of the DMSS data will allow for consideration of longitudinal information. A hypothetical association rule might be "anthrax vaccination is associated with being a serviceman aged 18–24 years." CDC notes that the challenge in using this technique is interpreting the association rules and identifying those that merit further investigation.

- *Factor analysis and clustering of VAERS reports* Factor analysis is another statistical technique that CDC is assessing for use in identifying clusters of adverse events that follow receipt of AVA or other vaccines. The occurrence of a cluster of adverse events reported by military personnel who received AVA can be compared with the occurrence of the same cluster of events in military personnel who received other vaccines. Measures of association can be obtained with chi-square or Fisher's exact tests.

To decide whether the hypotheses of possible associations between receipt of anthrax vaccine and certain adverse events generated by these analyses should receive further investigation, a systematic literature review will be conducted to determine whether the association has been reported and to evaluate the biologic plausibility of the association.

Committee Comments

The committee agrees that both VAERS and DMSS are valuable and essential resources for generating hypotheses regarding the occurrence of adverse events following vaccination, and that they should be routinely monitored for signals of adverse events related to use of AVA and all other vaccines administered to the military and civilian populations.

The committee was pleased to see greater attention being given to DMSS as a tool for hypothesis generation. Because the medical care records in DMSS databases are collected in a more systematic and complete fashion than are reports to VAERS, the DMSS databases may be better suited to the proposed application of data mining and other techniques of statistical analysis. Some of these analytic tools are relatively new, and their validity when applied to DMSS data must still be carefully tested. But the analyses proposed by CDC may provide a valuable opportunity to learn more about data mining and about the analytic uses of DMSS data.

One approach to testing data mining with DMSS data might be to conduct retrospective analyses to determine whether known associations between exposures and health outcomes can be detected. Such analyses would have to involve exposures that are systematically documented in a DMSS data set. Opportunities to study vaccine-related adverse events are currently limited because DMSS has complete vaccination data only for AVA. But the Air Force has recently completed work to enter into DMSS all immunization data from medical records for airmen on active duty. These data extend back as far as is recorded in individual medical records. Plans also call for eventually adding immunization records from the other services (Personal communication, J. Brundage, Defense Medical Surveillance System, July 11, 2002).

However, the committee has serious reservations about the proposed plans for various screening analyses of the VAERS data set using data mining and other statistical techniques. As the committee noted in its interim report, statistical analysis of VAERS data is challenging. As a spontaneous reporting system, VAERS is inherently incomplete and subject to reporting biases that are difficult to assess. The data may also be duplicative or inaccurate. The committee is concerned that statistical analysis of data from such systems is of questionable validity. CDC notes that other efforts are planned to increase the completeness and accuracy of VAERS reporting, especially as related to AVA vaccination, but the emphasis on increased reporting will not overcome the fundamental limitations of VAERS for certain types of analyses.

While there is growing interest in and use of data mining and related analytic techniques with VAERS (e.g., Niu et al., 2001) and other spontaneous reporting systems, these techniques still require further study to establish their validity and reliability when used with large, automated, multipurpose data systems such as DMSS, and even more so with a system like VAERS. The committee considers routine application of data mining techniques to VAERS data inappropriate unless those techniques are thoroughly evaluated in other, more complete data sets such as those in DMSS and are shown to be effective even in the face of the kinds of biases inherent in the VAERS data. If the use of data mining in DMSS can be validated, the availability of data on health outcomes following exposure to AVA in both DMSS and

VAERS may provide an unprecedented opportunity to use associations identified in DMSS in subsequent efforts to validate the use of data mining in VAERS.

It is possible that data mining techniques may be found to have the ability to detect more subtle or more complex associations than simpler analyses can. The committee notes, however, that AMSA's routine screening of DMSS data is already generating hypotheses related to AVA that have not yet been investigated.

Finding: The application of data mining and other statistical analysis techniques to screen data from VAERS and from DMSS data sets is still experimental.

Recommendation: Hypothesis generation using data mining and other statistical techniques for screening data should be tested and validated in DMSS or other structured data sets before being considered for use with VAERS. Only if these techniques can be validated with a structured data set and then with VAERS data should they be used to generate hypotheses from VAERS concerning adverse events and AVA.

Hypothesis Testing

Planned Activities

Hypotheses generated by the analysis of VAERS and DMSS data will be tested by the collaborative Analytic Unit being established at AMSA. The Analytic Unit will have access to the DMSS databases and to other medical records for military personnel who have received AVA and those who have not. These data can be used for various types of hypothesis-testing studies, including case-control or cohort studies or case-series analyses. Because the DMSS data resources appear similar to those of the civilian managed care organizations participating in CDC's collaborative VSD project, the Analytic Unit may be able to apply methods, such as survival analysis, that are being used in VSD studies. CDC notes the need to develop methods to map the coding system used in VAERS to identify adverse events (COSTART) to the ICD-9-CM[9] diagnosis codes used in the DMSS databases.

Committee Comments

The committee is pleased to see the evolving collaboration between CDC and DoD to facilitate the use of DMSS data for hypothesis testing. The DMSS databases are unique in that they contain relatively complete data on health care, AVA immunization, and personnel status for the active-duty military population—the group in whom AVA has been used most widely. Furthermore, as a product of the routine collection of administrative data, the DMSS data are fundamentally different from VAERS data, making them a good resource for testing hypotheses that may emerge from VAERS. But because DMSS will also be used to generate hypotheses, the committee notes the need for suitable plans to test those hypotheses with other data. Preliminary investigations, though, might include more detailed analysis of data from DMSS, including efforts that might involve the review of medical records.

Finding: DMSS is a uniquely valuable resource for testing hypotheses regarding medically significant health effects of exposure to AVA or other vaccines, especially those that might arise several months after vaccination but within the period of active duty.

In the committee's view, CDC should be placing much greater emphasis on the hypothesis-testing aspect of this portion of the Anthrax Vaccine Safety and Efficacy Research Plan. Reviews of VAERS and DMSS data have already generated hypotheses that require further investigation. Although AMSA conducted some preliminary analyses at the request of the IOM committee that reviewed the safety and efficacy of the anthrax vaccine for DoD (IOM, 2002), resource constraints limited the extent of those analy-

[9] ICD-9-CM refers to the *International Classification of Diseases, Ninth Revision, Clinical Modification*.

ses. Moreover, AMSA's primary mission is surveillance, not hypothesis testing. Therefore, CDC's establishment of the Analytic Unit at AMSA represents a real and valuable addition of resources to the effort to ensure that possible health risks associated with receipt of AVA are adequately studied.

Recommendation: CDC should work with DoD to follow up the signals regarding AVA that have already been generated by the review of VAERS reports and preliminary analyses of DMSS data on hospitalization and outpatient visits (see IOM, 2002).

The DMSS databases provide the opportunity to monitor the inpatient and outpatient health care provided to military personnel over the entire period of their active service. For those who receive AVA, this generally means that health care information is available for the period before vaccination, as well as for several months and potentially several years after vaccination.[10] In addition, comparable information is available for military personnel who do not receive AVA but do receive other vaccines. This makes DMSS data particularly valuable and appropriate for studies of medically significant adverse events that might be associated with AVA. DMSS, however, does not routinely capture information on milder adverse events for which medical care is not sought or that do not result in time lost from duty.

Recommendation: Analysis of DMSS data should be the primary approach for investigation of possible AVA-related health effects of medical significance that occur within the typical period of active duty following vaccination (perhaps as much as 3 to 4 years on average).

Investigation of concerns about adverse events that occur in the months and years after vaccinated military personnel leave active duty will require access to data sources beyond DMSS. The committee urges CDC, in support of its hypothesis-testing activities, to explore other data sources and possible ways to link them with DMSS data. The Millennium Cohort Study, for example, may provide a framework for studying morbidity and mortality in a defined group of military personnel, if it includes adequate numbers of participants who received AVA. In addition, concerns about premature or cause-specific mortality might be investigated using data from the Department of Veterans Affairs (VA). Deaths of military personnel could be tracked through resources such as the Beneficiary Identification and Records Locator Subsystem of the VA, the Social Security Administration, and the National Death Index.

The committee also emphasizes the importance of exploring the use of data from the VA health care system as an adjunct to DMSS for studies of morbidity. Although the VA health system serves only a small portion of the population of persons who have left military service, that population may be particularly well suited for identifying cases of unusual health problems. A new agreement between DoD and VA for greater exchange of health information (DoD, 2002; MacKay and Chu, 2002) may facilitate linkages between DMSS and VA health records.

Recommendation: To allow for analysis of health effects of AVA that might arise following the completion of active duty, CDC should investigate the use of DMSS data in conjunction with morbidity and mortality data from the Millennium Cohort Study and the health system of the Department of Veterans Affairs. Deaths of military personnel identified through DMSS could be tracked through resources such as the Beneficiary Identification and Records Locator Subsystem of the VA, the Social Security Administration, and the National Death Index.

The committee is concerned that insufficient priority is being given to the hypothesis-testing work that is to be done through the Analytic Unit being established at AMSA. The proposed funding level reflected in the version of the CDC–DoD Memorandum of Understanding provided to the committee (a total of $950,000 over 3 years) does not appear adequate to support the kind of analysis of DMSS data that will be necessary to investigate hypotheses that have already been generated by AMSA's routine screening of DMSS data and by the work of the IOM committee that reviewed the safety and efficacy of the

[10] Typical Army enlistment is 2 to 6 years (Grabenstein, 2001).

anthrax vaccine for DoD (IOM, 2002). Some of these analyses are likely to require time-consuming collection and examination of individual medical records, not just automated analysis of electronic records. Moreover, CDC's planned hypothesis-generating activities will only add to the demand for additional hypothesis-testing analyses of DMSS data.

Recommendation: Adequate resources (substantially more than can currently be identified from the CDC–DoD Memorandum of Understanding) should be made available to support the use of DMSS data for testing hypotheses regarding health effects related to AVA or other vaccine exposures.

Management and Oversight of Activities Related to Hypothesis Generation and Hypothesis Testing

Committee Comments

The committee also had concerns about the management and oversight of the hypothesis-generating and hypothesis-testing activities that CDC has described. These activities should be guided by an overall study plan or strategy to ensure an appropriate balance and coordination between hypothesis-generating and hypothesis-testing activities. Comprehensive oversight, based in CDC but allowing for coordination with DoD, is needed to establish priorities for this set of activities as a whole and for specific activities as well. Such oversight is also needed to address other matters, including ensuring timely and systematic hypothesis testing when hypotheses emerge. In the committee's view, the considerable emphasis placed on hypothesis generation through the use of experimental methodologies of data mining compared with the limited attention given to hypothesis-testing activities illustrates the lack of overall guidance and priority setting for these activities.

The materials from CDC do not provide a clear indication that this component of the AVA research program currently has the overall planning and guidance that the committee sees as necessary. Because DMSS is such a critical resource for both hypothesis generation and hypothesis testing, ongoing coordination between CDC and DoD seems essential. In addition, the committee believes that CDC's hypothesis-testing activities would benefit from a periodic assessment by outside experts who could provide advice on matters such as study design and analytic techniques, as well as the priorities for the analyses. The project timeline (CDC, 2002j) refers to the establishment of an Analytic Unit Advisory Committee in July 2002, but no information was provided to the committee concerning the anticipated membership or activities of this group.

Finding: An overall study plan or strategy is needed to guide CDC's use of VAERS, DMSS data sets, and other data sources for hypothesis-generating and hypothesis-testing activities related to AVA.

Recommendation: CDC, working with DoD, should establish a staff team with overall responsibility for the review and analysis of VAERS and DMSS data for both hypothesis generation and hypothesis testing related to AVA.

Recommendation: A committee of nongovernmental experts should be established to periodically advise CDC on plans and priorities for the analyses of data from DMSS and other sources to test hypotheses regarding health effects related to AVA.

POSSIBLE ROLE OF ALUMINUM HYDROXIDE ADJUVANT IN AVA-ASSOCIATED ADVERSE EVENTS

Potential Research Topics

CDC presented to the committee a brief review of issues related to aluminum-containing adjuvants and adverse events (CDC, 2002l). Aluminum is one of the most abundant elements on earth, and humans are routinely exposed to it through sources such as drinking water, medications (e.g., antacids), and deodorants. Little is known about the toxicology of injected aluminum, and human studies of the clearance of aluminum have been limited to patients with chronic renal insufficiency.

Aluminum compounds are used as adjuvants in some vaccines to enhance the immunogenicity of the product. AVA uses aluminum hydroxide as an adjuvant, and several other vaccines routinely administered to children and adults also use adjuvants containing aluminum. These vaccines include the diphtheria and tetanus toxoids and pertussis vaccine (DTP), other vaccines containing tetanus toxoids, and hepatitis B vaccine. While vaccine adjuvants containing aluminum have been used for many years, they have been associated with some local adverse events, such as erythema, subcutaneous nodules, skin allergy, and skin inflammation at the injection site. Adverse events of this type also occur in persons who receive AVA, but studies have not been done to establish whether the adverse events observed following receipt of AVA are related to the adjuvant.

Recently, it has been suggested that aluminum-containing vaccine adjuvants might be associated with a condition that has been labeled macrophagic myofasciitis (MMF) (Gherardi et al., 1998, 2001). The symptoms attributed to this condition include myalgias, arthralgias, muscle weakness or tenderness, and fatigue. Aluminum has been found in tissue biopsies of persons considered to have the condition, but tissue biopsies from suitable control groups have not been tested. Thus, it remains uncertain whether the presence of aluminum in tissue biopsies of persons said to have MMF is a sign of pathology or only a coincidental finding.

CDC (2002l) listed five possible research questions that might be investigated:

1. Are subcutaneous nodules following AVA vaccination caused by subcutaneous accumulation of aluminum hydroxide adjuvant?
2. Is the gender differential in the occurrence of adverse events observed following AVA vaccination associated with impaired local clearance of aluminum hydroxide adjuvant?
3. Are individuals (particularly women) with iron deficiency anemia more prone to develop injection-site adverse events, including subcutaneous nodules, following AVA vaccination?
4. Are individuals (particularly women) with iron deficiency anemia more prone to develop systemic adverse events following AVA vaccination?
5. Is macrophagic myofasciitis (MMF) a condition associated with AVA?

CDC assigned this topic a lower priority than the other proposed studies and noted in the materials provided to the committee that no study proposals or protocols had been developed.

Committee Comments

The committee acknowledges that there are concerns that the aluminum adjuvant in AVA might contribute to certain types of adverse events or adverse events in certain people. However, a summary of a May 2000 workshop on aluminum in vaccines (Eickhoff and Myers, 2002) indicates that the pervasiveness of aluminum in the environment and the limited understanding of the toxicology and kinetics of injected aluminum adjuvants pose serious scientific and practical challenges to efforts to investigate health effects that might be associated with a specific source of exposure, such as AVA. Furthermore, the preliminary nature of the evidence concerning MMF suggests that it is premature to investigate whether re-

ceipt of AVA is associated with that condition. Given these constraints, the committee does not consider it appropriate for CDC to pursue research on any of the proposed questions as part of the Anthrax Vaccine Safety and Efficacy Research Plan.

Finding: Widespread environmental exposure to aluminum makes it difficult to conduct a study of potential adverse effects of exposure to the aluminum hydroxide adjuvant/adsorbant in AVA.

Finding: The significance of the presence of aluminum in tissue biopsies of persons diagnosed with the condition called macrophagic myofasciitis has not been established.

Recommendation: The study of the possible role of the aluminum hydroxide adjuvant in adverse events following receipt of AVA should be eliminated from the CDC research program.

REPRODUCTIVE HEALTH

CDC included among its research questions whether receipt of AVA is associated with adverse effects on women's reproductive health. The committee agrees that this is an important concern if the vaccine is to be routinely administered to women in the military, or if circumstances should require vaccination of civilian women. CDC notes that several DoD studies are investigating aspects of this topic, including fertility rates following vaccination and rates of birth defects among vaccinated women.[11] The committee notes that none of the CDC research studies directly address the relationship of AVA vaccination with reproductive health.

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[11] DoD policy exempts from vaccination women known to be pregnant, but some women with early unconfirmed pregnancies may be vaccinated inadvertently.

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6

Proposed Studies on the Acceptability of the Anthrax Vaccine

While the issue of acceptability is not explicit in the congressional mandate to the Centers for Disease Control and Prevention (CDC) for research on the anthrax vaccine, it is an important consideration. When people are reluctant or unwilling to accept a vaccine, it clearly poses important obstacles to achieving the protection that the vaccine might afford. Concerns on the part of some service members and members of the public have affected the acceptability of Anthrax Vaccine Adsorbed (AVA) since the Department of Defense (DoD) implemented the Anthrax Vaccine Immunization Program (AVIP). These concerns are reviewed briefly in Chapter 2 and in greater detail in another report from the Institute of Medicine (IOM, 2002).

A study in Air National Guard and Air Force Reserve forces indicated that the level of concern about AVA was high (GAO, 2000). Similarly, a CDC pilot study of vaccine providers and health care administrators at an Air Force base in August 2000 found that 20 percent of the respondents were concerned about the safety of the vaccine and that only 15 percent believed they were likely to be exposed to anthrax spores (CDC, 2002a). These studies were carried out in the context of a service-wide mandatory AVA vaccination program at a time when the public had only a limited awareness of the potential threat of exposure to anthrax spores.

Circumstances have changed, however. Bioterrorist events in the fall of 2001 resulted in the exposure of large numbers of civilians to anthrax spores and five deaths from inhalational anthrax. In addition, new lots of AVA have been released by FDA following approval of renovations of the manufacturing facility (Masiello, 2002). An IOM review of the available evidence about the vaccine has found the vaccine's safety to be comparable to that of other adult vaccines (IOM, 2002). Finally, the current vaccination program is limited to those military personnel "at higher risk whose performance is essential for certain mission critical capabilities" (Wolfowitz, 2002). The committee reviewed CDC's proposed studies on acceptability in light of the current circumstances.

OBJECTIVES AND CRITICAL RESEARCH QUESTIONS FOR CDC RESEARCH ON THE ACCEPTABILITY OF THE ANTHRAX VACCINE

CDC's stated objectives for the acceptability component of its anthrax vaccine research program are displayed in Box 6-1. At the request of the committee, CDC also identified a set of critical research questions, shown in Box 6-2.

CDC intends to investigate the acceptability of the anthrax vaccine by identifying concerns about it among military vaccine recipients through large surveys on knowledge, attitudes, and beliefs (KABs) powered to yield estimates by service and by subgroups within each service; a patient satisfaction survey;

BOX 6-1
CDC Objectives for Research on the Acceptability of the Anthrax Vaccine

- KAB [knowledge, attitudes and beliefs] surveys, patient satisfaction survey, and other assessment tools will be developed and used to identify concerns about anthrax vaccination among military vaccine recipients. Research partners will include the DoD, the VHC Network, and the Research Triangle Institute (RTI).
- In collaboration with AVIP, VHC Network, and others, knowledge gained from the KAB surveys and the efficacy and safety studies will be used to:
  - Develop, promote, and provide training that will optimize and standardize procedures and quality assurance practices for the administration of AVA.
  - Develop strategies and training materials to help improve the acceptability of AVA and military immune readiness, in general.
- Train NIP [National Immunization Program] Hotline and other CDC Hotline personnel to respond effectively to military and public questions and concerns about AVA.
- A repeat KAB survey and other assessment tools will be used after education and training interventions to measure changes in KABs and impact of interventions.

SOURCE: CDC, 2002b, p. 14.

BOX 6-2
Critical Research Questions Regarding the Acceptability of the Anthrax Vaccine, as Identified by CDC

- What percentage of military personnel have a concern regarding AVA?
- What are the specific concerns regarding the vaccine?
- Does prior experience with AVA or other vaccines influence current knowledge, attitudes, and beliefs (KABs)?
- Do differences in KABs and the level of concern about the AVA vaccination exist based on the following factors: gender, officer/enlisted status, branch of the military, active duty or guard/reserve status, and vaccination history?
- What sources of anthrax vaccine information are the most credible?
- Do KABs and the level of concern regarding the anthrax vaccine change over time?
- Are planned or unplanned interventions responsible for changes in KABs and level of concern regarding AVA among military personnel?
- Is there an association between educational materials and changes in KABs? Is it important for educational materials to be written by an independent source?
- Are military personnel familiar with Vaccine Adverse Event Reporting System (VAERS) reporting and what percent report follow-up actions when complications occur?

SOURCE: CDC, 2002c.

and other assessment tools. Detailed documentation of the acceptability of the vaccine within the military population is the major thrust of the research program as planned. However, the committee believes that a different prioritization is appropriate. Rather than emphasizing detailed measurements of the level of concern about the anthrax vaccine in surveys with large numbers of participants, it would be more appropriate to focus on learning how educational interventions can improve acceptability. While the development

of strategies and training materials that are aimed at increasing the acceptability of the vaccine is listed among the CDC research objectives, it is given little attention in the protocols provided to the committee.

Similarly, the committee disagrees with the relative priorities that have been assigned to the critical research questions. The committee considers the questions related to the development of interventions to be as or more important than the questions currently emphasized by CDC regarding determining the percentage of military personnel with concerns regarding AVA. While documenting the concerns of military service members about the vaccine is important, this information is most useful in the context of learning how these concerns might be met through interventions. Thus, the committee views developing and testing interventions as a more appropriate focus for CDC's efforts than producing exhaustive information on the percentages of service members with concerns. The need for such a change in emphasis is discussed further in conjunction with the proposals for individual studies.

SURVEY OF KNOWLEDGE, ATTITUDES, AND BELIEFS REGARDING THE ANTHRAX VACCINE AMONG MILITARY PERSONNEL

The stated goal for this portion of CDC's research on the acceptability of the anthrax vaccine is to assess the KABs of military service and health care personnel regarding AVA (CDC, 2002a,d). Representative surveys of the military population are planned for two different time points to provide an understanding of the factors influencing perceptions of the safety and efficacy of the anthrax vaccine and to direct the development of appropriate educational materials. CDC contracted with Research Triangle Institute (RTI) to devise a study design to gather information from a representative sample of the U.S. military's active and reserve populations. The specific aims of the study are shown in Box 6-3.

BOX 6-3
Specific Aims of the Survey of Knowledge, Attitudes, and Beliefs Regarding the Anthrax Vaccine Among Military Personnel, as Identified by CDC

Primary specific aims:

- Determine the percentages of currently assigned military personnel who have a concern (by level of concern) regarding the anthrax vaccine.
- Describe the specific concerns regarding the vaccine.
- Determine if prior experience with AVA or other vaccines influence current KABs.
- Determine if differences in KABs and the level of concern about the AVA vaccination exist, using univariate and multivariate techniques, based on the following factors: gender, officer/enlisted status, branch of the military, active duty or guard/reserve status, and vaccination history.
- Assess familiarity with Vaccine Adverse Event Reporting System (VAERS) reporting and whether follow-up actions were taken when complications were reported.

Secondary aims:

- Determine if KABs and the level of concern regarding the anthrax vaccine change over a 2-year period.
- Determine what planned or unplanned interventions may be responsible for changes in KABs and level of concern regarding AVA among military personnel.
- Assess potential associations between CDC educational materials and changes in KABs, and assess the importance of an independent source of anthrax vaccine information.

SOURCE: CDC, 2002a, p. 1.

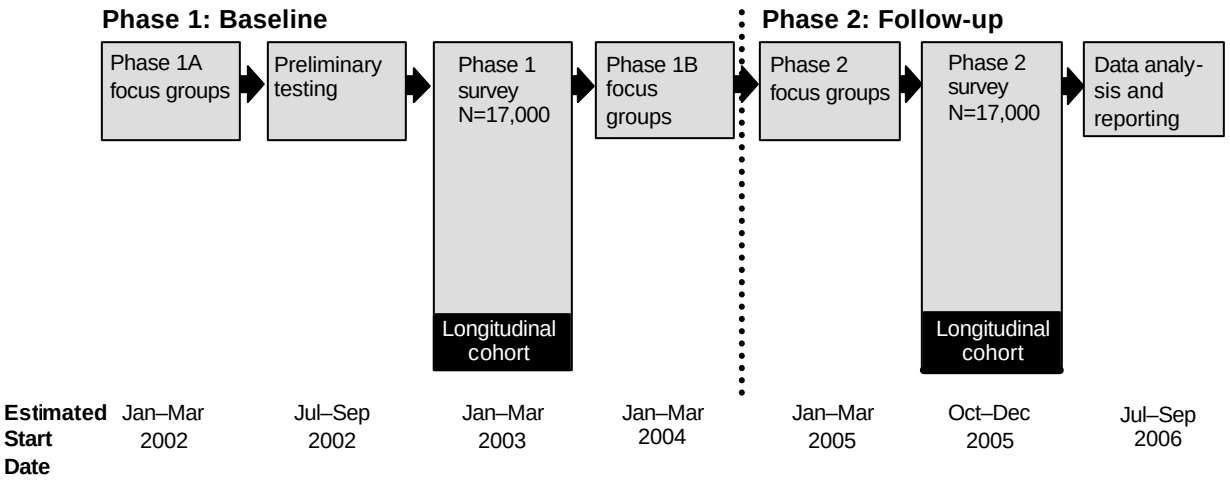

FIGURE 6-1 Proposed components and estimated timeline for the KAB survey of military personnel regarding the anthrax vaccine

Study Design

RTI's plan for this study involves two phases that rely on complementary focus groups and surveys. Figure 6-1 offers a schematic illustration of the timing of the focus groups and surveys, as described in the draft proposal.

Focus Groups

Two phases of focus group meetings are planned to aid in the development of the survey and to test the educational materials that CDC develops on the anthrax vaccine. RTI will recruit focus group participants from geographically diverse military installations. To ensure that the qualitative information gathered will provide representative viewpoints of the U.S. military's active and reserve populations, plans call for approximately one-third of the total participants to be non-Caucasians. Twenty-six focus groups are planned for the first phase to make it possible to segment the groups by gender, experience with AVA, medical training, military branch or component, and rank. Focus groups in phase 1 of the study design are further subdivided into phase 1A and phase 1B.

Phase 1A focus groups will be used to gather information that can be applied to the development of the survey for phase 1 of the study, as well as to explore the KABs of military personnel regarding their sources of information about AVA and the perceived credibility of these sources. In phase 1A, the focus groups will also be used to determine which forms of communication participants prefer for receiving educational information about AVA.

Educational materials designed on the basis of the phase 1A focus group discussions will be tested 12 to 15 months later in phase 1B. Phase 1B focus groups will be exposed to an educational message about AVA followed by a series of semi-structured, open-ended questions about how they received the message. Focus group discussions that result from the questions will be used to explore ways to revise and refine potential educational messages. A structured questionnaire will also be administered to participants to gauge their knowledge about AVA.

Phase 2 will use eight focus groups that are scheduled to begin meeting shortly after the completion of phase 1B focus groups. The groups will be designed to distinguish key changes from earlier focus groups in the KABs of participants regarding AVA. Information collected in the phase 2 focus groups

will be used to develop questions for the complementary phase 2 survey, scheduled to commence shortly after completion of the focus groups.

RTI will provide CDC with brief summaries of the individual focus groups, including participants' sociodemographic characteristics, and will compile the findings from the focus groups in both phases 1 and 2 on the educational needs of military personnel related to AVA and AVA vaccination. On the basis of those findings, RTI will recommend how CDC should address the unmet educational needs of military personnel, propose methods to increase the acceptability of AVA, and suggest the preferred information and media sources of military personnel.

Surveys

Using information gathered from the focus groups, RTI will develop two surveys (repeated cross-sectional surveys) that will be administered approximately 2 years apart. As with the focus groups, survey participants will be a randomly selected representative sample of U.S. active and reserve military personnel. Each survey will be administered to approximately 17,000 military personnel who will complete the survey form in classroom settings on military bases. The sample determination, based on stratified random sampling with proportional allocation, was designed to assure representation of all service and regional components of the military population. The phase 1 survey will be administered after the phase 1A focus groups and after the resumption of the AVIP. The phase 2 survey will be administered after the phase 2 focus groups.

The survey in phase 1 will be used as a baseline to gather key information from the participants regarding their KABs toward AVA and other vaccines and their exposure to information about vaccines. The phase 1 survey will also determine if respondents' KABs toward AVA and other vaccines are influenced by prior experience with vaccines. A measurement of KABs regarding military vaccines other than AVA will be included to allow for comparison and contrast to AVA. In addition, the baseline survey will be used to estimate participants' perceptions of the frequency and severity of AVA-related complications and to determine the need for CDC-developed AVA educational interventions. The survey will be stratified by gender, anthrax vaccination history, and enlistment and duty status.

The follow-up survey (phase 2 survey) will include a longitudinal comparison to assess temporal changes in KABs regarding the anthrax vaccine. For the longitudinal comparison, selected individuals will participate in both the baseline and follow-up surveys. Their responses will be evaluated to determine whether the observed temporal changes in KABs are associated with interventions alone or with other baseline or societal factors. The analysis will control for anthrax vaccination status.

Before beginning the surveys, RTI plans preliminary tests to ensure the validity of the survey instrument. The testing to validate the survey instrument will include preliminary cognitive testing interviews; a pilot study for each of the active services, a National Guard unit, and a reserve unit; and a psychometric analysis test. Six questions from the Balanced Inventory of Desirable Responding (BIDR)—a 40-question survey that measures self-deceptive enhancement and impression management—will be incorporated into the phase 1 and 2 surveys as a covariate to control for social desirability bias in survey responses. The preliminary testing will also validate the BIDR questions included in the survey.

Committee Comments

As designed and described in the summary and protocol provided by CDC, this study will provide a thorough assessment of military KABs regarding the anthrax vaccine. The design phase of the study has been expanded to include cognitive and psychometric tests and a pilot survey, as recommended by this committee in its interim report (IOM, 2001). The summary and protocol raise questions, however, about the overall objectives or motivation for the study and the need for the very large sample size proposed. Although the committee found in its interim report that the rationale for investigating the KABs of service personnel was appropriate, the additional information reviewed by the committee in preparing the present

report does not justify the need for the level of detail that is driving the use of a study population of 17,000 persons.

It will certainly be helpful to know more about the concerns of military personnel regarding the anthrax vaccine, vaccines in general, and some of the influences on and sources of this concern, but this information should not be an end in itself. Since scientific experts have not found evidence to link AVA with adverse events other than immediate-onset reactions typical of those observed with other vaccines administered to adults (IOM, 2002) and because intelligence assessments indicate that U.S. forces face a real threat of exposure to biological weapons (Wolfowitz, 2002), this licensed vaccine is likely to continue to be used by the military and for selected civilian populations.

Thus information about knowledge, attitudes, and beliefs about AVA is valuable to the extent that it can facilitate or further some constructive action to increase the acceptability of the vaccine. The CDC protocol, however, does not indicate that the results of the phase 1 survey will be used to guide the formulation of different intervention strategies. Furthermore, such a large study could create a burden on the many respondents and on military units, which would have to aid in scheduling times and locations for participants to complete the survey. The available resources might be better applied to the development of intervention materials.

The protocol notes that the assessment of CDC educational materials is a secondary aim for the study. If the ultimate motivation for the study is the development or refinement of such materials, there appears to be a lack of planning toward this end in the study design. Specific materials could be drafted at the start, and tested and refined with focus groups rather than after an exhaustive survey. Materials would be targeted for military personnel and their family members, as well as vaccine providers and other health care providers likely to care for those with concerns about the vaccine. A smaller sample size for the survey, on the order of 3,000, would seem adequate to provide data regarding KABs for this purpose. The survey could also be enhanced by including a question about potential new anthrax vaccines, in addition to the planned questions about military vaccines other than AVA. The focus groups and survey might also aid in the development of effective educational materials by gathering information on how the respondents prefer to hear health messages and on how they view alternative approaches to achieving acceptance.

Concerns have been expressed (Hubbell, 2002) that the survey will lack credibility because military personnel will doubt the confidentiality of their responses and therefore will not feel free to answer the survey questions honestly. The committee agrees that the study is vulnerable to such concerns and recognizes that the survey designers can do only a limited amount to address them. While assurances can be given to study participants that their answers will remain individually anonymous, results may be reported at group or unit levels. Participants may feel constrained to provide responses that will not discredit their group or unit. RTI plans to use questions from the BIDR to control for potential social desirability bias in responses, but this cannot address the overall problem of concerns about confidentiality.

The committee was also concerned about the study's timeline. The phase 1 survey is anticipated in 2003, with the report on the entire study to be completed by 2006. Since the next 4 years may bring changes in the way the current anthrax vaccine is administered or even see approval of a new anthrax vaccine, it is important that the study gather information to facilitate new materials or interventions relevant to a potential new anthrax vaccine or military vaccines more generally.

Finding: With its large sample size, the current design of the study of knowledge, attitudes, and beliefs regarding AVA primarily addresses the acceptability of the vaccine among military personnel. Further documentation of the prevalence of attitudes and beliefs regarding the vaccine is unlikely to significantly advance the acceptability of the vaccine, which should be the major goal. Instead, qualitative research techniques such as focus groups and smaller-scale surveys can be used to determine the breadth, depth, and underlying reasons for the attitudes and beliefs regarding AVA. This information can serve as the basis for targeted interventions, the impact of which can be assessed with subsequent surveys.

Recommendation: In view of the study timeline and research needs, CDC should modify the design of the KAB study of military personnel to focus on more timely development of educational interventions and the evaluation of their impact on the acceptability of AVA and a broader range of vaccines, including a new anthrax vaccine.

The draft protocol provided to the committee indicates that the focus groups used to gather information to design the survey will be assembled so that enlisted personnel, enlisted women, Reserve and National Guard units, health care personnel, and officers are each represented by a separate group (CDC, 2002a). Participants will be drawn from each main branch of the military. The study design appropriately takes gender into account in the plans for the focus groups. The committee notes that minority racial or ethnic groups may also have different opinions about AVA that they might not feel free to express in a heterogeneous group. Therefore, the committee recommends a focus group design that takes different racial and ethnic groups into account.

Finding: Potential differences between racial and ethnic groups in knowledge, attitudes, and beliefs about AVA and military vaccines generally may be important.

Recommendation: CDC should design the focus groups and preliminary survey to take into account different racial and ethnic groups.

SURVEY OF CIVILIAN AND MILITARY HEALTH CARE PROVIDERS REGARDING THE ANTHRAX VACCINE AND THE REPORTING OF POSSIBLE VACCINE-ASSOCIATED ADVERSE EVENTS

This study is planned to obtain representative data on the knowledge, awareness, attitudes, and practices of both military and civilian health care providers regarding the reporting of adverse events following immunization to the Vaccine Adverse Event Reporting System (VAERS) (CDC, 2002e). The study is also intended to obtain information on providers' general knowledge of and attitudes towards anthrax vaccination. Information obtained from the study will be applied to the development of appropriate vaccine benefit and risk communication materials, including educational and promotional materials targeted to providers regarding anthrax vaccine safety and reporting of adverse events. CDC also anticipates gathering information from the participants that might be used to improve VAERS from the reporter's perspective.

Study Design

Limited detail about this study was available in the information provided to the committee. According to the study summary, the survey of health care providers is to be carried out in two phases through a contract with RTI. In the first phase, RTI will recruit military and civilian health care providers from selected sites in eight geographically diverse areas to ensure multiple viewpoints. The focus groups will be used to collect qualitative data from health care providers about reporting of adverse events to VAERS following immunization. Preselected focus groups of military health care personnel participating in the KAB survey on AVA (discussed above) will be asked additional questions about adverse event reporting.

The second phase of the study will consist of a mail-out survey of military and civilian physicians. Three study populations will be targeted: active-duty military physicians who are likely to provide anthrax vaccine and other vaccines; civilian physicians in solo or two-physician practices who are likely to provide vaccines; and civilian physicians in a group practice who are likely to provide vaccines. Military physicians will be selected proportionately by the region of the country in which they are stationed and by their branch of service. Civilian physicians selected to participate in the survey will be in office-based practices in the same cities as major military facilities, under 65 years of age, and have a primary specialty that would make them likely to administer vaccines.

The survey instrument will be a self-administered questionnaire that will require 15 to 20 minutes to complete and that can be processed using a scanning optical-mark reader. Results from the focus groups of phase 1 will be used to add to or modify existing survey instruments to develop the questionnaire. The mail-out survey will integrate questions about office practices and technology, vaccine-related adverse event reporting, and knowledge and attitudes regarding the anthrax vaccine and other vaccines. In addition, each questionnaire will be used to assess the sociodemographic characteristics of the respondent.

To provide sufficient sample size to detect differences of interest between the groups, RTI will mail the surveys to 538 participants from each of the three health provider categories. According to CDC, the survey response rate is expected to be 65 percent following multiple waves of mailings and phone calls.

Committee Comments

CDC has responded to the committee's previous recommendation (IOM, 2001) to broaden the survey beyond a narrow focus on KABs regarding VAERS to include KABs about the anthrax vaccine. The committee endorses this modification and notes that broadening the survey still further to provide information about health care provider KABs regarding vaccination in general would provide additional improvement. In the committee's view, the survey should include not only providers who administer vaccines, but also those who deliver care and advice when a service member has a concern or adverse event following vaccination.

Given the effort and time that will go into the survey, the committee believes that it should be designed to produce results that will be applicable to the current anthrax vaccine and to potential new anthrax vaccines; to vaccines more generally; and to mandatory vaccination, such as that required by the military. This information could be very useful for the development and targeting of educational and promotional materials for health care providers on anthrax vaccine safety and on the reporting of adverse events, as described in the study summary.

It was not clear from the draft protocol why the civilian health care providers were stratified by size of practice. The committee cautions that this may unnecessarily handicap the analysis by limiting the size of the groups.

Finding: As proposed, the survey of civilian and military health care providers has a focus on knowledge, attitudes, and beliefs concerning VAERS and vaccination with AVA. Additional questions oriented toward the development of educational materials concerning AVA and other vaccines, immunization, and adverse events could broaden its usefulness. In addition, further articulation of links between the study and development of educational materials is needed.

Recommendation: In addition to gathering information on KABs about VAERS and the current anthrax vaccine, CDC should modify the survey of health care providers to study KABs about a new anthrax vaccine, other military vaccines, and vaccines in general, with a focus on information useful for timely development and testing of appropriate educational materials. The study population should include health care providers who may treat service members with adverse events following vaccination as well as those who administer vaccines.

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7

Summary Assessment of the CDC Anthrax Vaccine Research Plan

The charge to this Institute of Medicine (IOM) committee was to advise the Centers for Disease Control and Prevention (CDC) on the completeness and appropriateness of its response to a congressional mandate to study the safety and efficacy of the anthrax vaccine. The vaccine currently licensed for human use is Anthrax Vaccine Adsorbed (AVA). The congressional mandate (included in Public Law No. 106-113) specified that CDC was to address "(1) risk factors for adverse events, including differences between men and women; (2) determining immunological correlates of protection and documenting vaccine efficacy; and (3) optimizing the vaccination schedule and routes of administration to assure efficacy while minimizing the number of doses required and the occurrence of adverse events."

Over the course of the committee's five open meetings, CDC provided written information and oral presentations about its developing anthrax vaccine research program. The committee also heard oral presentations and received written materials from service members and others with concerns about the safety or efficacy of the anthrax vaccine. The committee issued an interim report in July 2001, 8 months into its work (IOM, 2001). Meanwhile, the CDC research program and plans for individual studies continued to evolve over the course of the committee's work. To make its final assessment, the committee requested written materials from CDC that would provide a comprehensive description of the objectives and design of the proposed research studies as of February 2002. The committee also requested that CDC identify critical research questions related to the efficacy, safety, and acceptability of the anthrax vaccine. This final report is based on the committee's deliberations, with significant emphasis on its review of the materials provided by CDC in February 2002. A subset of these key documents is found in Appendix C.

CDC RESEARCH PLAN

Responsiveness to the Congressional Mandate

After examining the components of the CDC anthrax vaccine safety and efficacy research program specifically in terms of the congressional mandate, the committee finds the CDC response to be generally complete and appropriate. The clinical trial is appropriate and satisfactorily designed to address the congressionally mandated charge to optimize the vaccination schedule and the route of vaccine administration. The nonhuman primate studies conducted in conjunction with the human clinical trial should largely address the challenge of determining immunological correlates of protection and documenting the efficacy of the vaccine.

The committee's qualifications regarding the research plan arise from the lack of passive protection studies in the determination of immunological correlates of protection (discussed in Chapter 4 and re-

viewed briefly below) and potential constraints from small sample sizes on the investigation of differences between men and women in risk factors for adverse events that occur at the time of vaccination (described in Chapter 5 and recapitulated below). Although the research program also lacks satisfactory plans for investigating adverse health effects that might be rare or become evident many years after vaccination, the committee has seen no evidence that such studies should be a high priority. These limitations do not alter the committee's conclusion that the CDC research program as planned includes most of the studies needed to provide a strong and appropriate response to the congressional mandate.

When considered in its entirety, however, the CDC anthrax vaccine research program includes elements that the committee considers to be of lower priority, and some that should not be carried out as planned (see Table 7-1). These concerns have been detailed in chapters 4, 5, and 6 and are summarized below.

Finding:

1. **With respect to the tasks specifically outlined in the congressional mandate, CDC's research response is generally complete and appropriate.**
2. **When considered as a whole, however, the research program has elements that are of low priority and other elements that are inappropriate and should not be carried out as planned.**

Research Studies and Priorities

Since the release of the interim report from this committee, CDC has devoted considerable and commendable effort to the development of the studies that make up the research plan. CDC grouped these studies into the categories of efficacy, safety, and acceptability. The committee's assessments of the research objectives and studies planned in each of these categories are discussed in detail in the preceding chapters and are summarized below and in Table 7-1.

In making its assessments, the committee also considered the priority to be given to individual studies within the overall research program. While CDC designated all of the proposed studies as of high priority, the committee concluded that two efforts should be considered of the highest priority. One is the clinical trial and its related studies, which are aimed at identifying correlates of protection and establishing the optimal vaccination schedule and route of vaccine administration in terms of achieving a satisfactory immune response and minimizing the occurrence of adverse events. The other studies of highest priority are those exploiting the resource provided by the Defense Medical Surveillance System (DMSS) for generating and testing hypotheses about medically significant adverse events that might be associated with the anthrax vaccine. The committee also concluded that several studies had a low priority or should not be conducted at all.

Efficacy

Overall, the efficacy research program includes a strong set of studies (Human Clinical Trial, Nonhuman Primate Studies, Immune Correlates of Protection Studies) that are of high priority and are well designed to address many of the most important critical research questions and the congressional mandate. Aspects of the efficacy program pertaining to correlates of protection were viewed as particularly relevant, given that new anthrax vaccines are in development. Yet, the committee also notes important limitations of the research on the efficacy of AVA. Most importantly, the program lacks studies of passive protection in rhesus macaques. The committee views these studies as a high priority. They are necessary to determine the level of antibody required to achieve protection from disease caused by anthrax spores (see Chapter 4). The committee also notes the need for studies to evaluate the effect of inoculum size on the protection afforded by AVA. Such studies would be a natural follow-up to studies of passive protection that determined protective levels of antibodies. Their importance was made clear by the bioterrorist actions in the fall of 2001.

TABLE 7-1 Committee Prioritization of Studies in the CDC Research Program on the Safety and Efficacy of the Anthrax Vaccine

Committee Priority	Studies Proposed by CDC
High	Human Clinical Trial (Chapter 4, p. 47, and Chapter 5, p. 61)
	Nonhuman primate vaccine dose ranging, immunogenicity and challenge trial (Chapter 4, p. 50)
	Immune correlates of protection studies (antibodies only) (Chapter 4, p. 52)
	Hypothesis testing using data from the Defense Medical Surveillance System (Chapter 5, p. 76)
Medium	Vaccine Healthcare Center (VHC) study of adverse events occurring soon after receipt of AVA (Chapter 5, p. 68)
Low	Human leukocyte antigen substudy (Chapter 4, p. 48)
	Immune correlates of protection studies (other than antibody-based) (Chapter 4, p. 53)
	VHC-based study of the effect of women's hormonal phase on the occurrence of adverse events following immunization with AVA (Chapter 5, p. 72)
	Hypothesis generation from use of data mining and other statistical techniques to screen data from the Defense Medical Surveillance System (Chapter 5, p. 76)
Not Recommended	Nonhuman primate-immune correlates of protection substudy involving multiple invasive procedures (e.g., biopsies) (Chapter 4, p. 54)
	Textile mill worker follow-up study (Chapter 5, p. 66)
	VHC-based study of the effect of AVA vaccination on health-related quality of life (Chapter 5, p. 71)
	Hypothesis generation from use of data mining and other statistical techniques to screen data from the Vaccine Adverse Event Reporting System (Chapter 5, p. 76)
	Possible role of aluminum hydroxide adjuvant in AVA-associated adverse events (Chapter 5, p. 80)
Not Recommended; Committee recommends a related study (see text and Table 7-2)	Survey of knowledge, attitudes, and beliefs regarding the anthrax vaccine among military personnel (as proposed by CDC) (Chapter 6, p. 87)
	Survey of civilian and military health care providers regarding the anthrax vaccine and the reporting of possible vaccine-associated adverse events (as proposed by CDC) (Chapter 6, p. 89)

In contrast, the committee concluded that other proposed studies have a relatively low priority. These studies include the analysis of genetic polymorphisms of the human leukocyte antigen system as well as many of the assays that focus on cellular aspects of immunity as part of the proposed studies of the immune correlates of protection. The committee questions the usefulness of the multiple lymph node biopsies, bone marrow biopsies, and bronchoalveolar lavage planned for a subset of the animals in the nonhuman primate study since the repeated procedures and the accompanying need for anesthesia may alter the observed responses. The committee recommends that these studies not be continued in their current form.

Safety

Regarding the studies related to the safety of the anthrax vaccine, the committee found that the human clinical trial should provide important information about the risk factors for common adverse reactions that occur soon after vaccination, including differences in reaction rates related to subcutaneous (SQ) versus intramuscular (IM) administration of the vaccine. With data from the clinical trial it should also be possible to examine differences between men and women in the occurrence of immediate-onset adverse events and to compare those results with findings from other studies (CDC, 2000; Hoffman et al., submitted for publication; Pittman et al., 2002). The clinical trial will include an investigation of the effect of women's hormonal phase on the risk of adverse events, but additional studies beyond those described by CDC would be needed to better understand the reasons for any differences that might be found between men and women in the occurrence of adverse events. The committee also cautions that the SF-36 health status survey, if used by itself, is unlikely to be a satisfactory tool for the proposed evaluation of the association between receipt of AVA and changes in health-related quality of life in the clinical trial.

The committee recommends against the retrospective cohort study intended to investigate potential chronic health effects or later-onset adverse events following anthrax vaccination. As proposed, the study of former textile mill workers is highly unlikely to be able to detect any important later-onset health effects that might be associated with anthrax vaccination and would carry the risk of producing spurious positive or negative associations. The study faces these problems because of the difficulty in finding truly comparable control groups and because of the relatively small size of the study population and the large number of variables in the planned analyses. Conducting the study poses the risk of generating unwarranted health concerns among the participants, without medical or scientific benefit.

One of the proposed cohort studies to be conducted through the Vaccine Healthcare Center (VHC) Network could, with a study population comparable in size to that of the clinical trial, provide useful postmarketing-type data to confirm the rates observed in the human clinical trial of common adverse events that occur soon after vaccination. With the plans to seek approval from the Food and Drug Administration for a change from SQ to IM administration of AVA, the study must be initiated promptly to include the planned comparisons of rates of adverse events with SQ and IM administration.

The committee notes that the proposed study is not well suited to monitoring the occurrence of less common, medically significant conditions that may not be seen during a clinical trial. Monitoring the occurrence of these events would require use of a much larger study population (10,000 or more participants). It would also require a control group whose members have not received AVA and who are comparable in initial health status to the population that received AVA. Identifying a suitable control group would be challenging because receipt of AVA will generally be related to deployment (Wolfowitz, 2002). Deployed personnel are likely to be healthier on average than nondeployed personnel because health problems may disqualify an individual from deployment.

For several reasons, the plans for a VHC-based study to assess the effect of AVA vaccination on health-related quality of life using the SF-36 health survey do not appear feasible. When used by itself, the SF-36 has limitations in distinguishing differences between generally healthy populations. It will also be challenging to follow study participants who are likely to have been deployed. In addition, it may be difficult to distinguish any changes in health status related to AVA from those related to deployment. Health status might also be affected by various other medications and vaccines received in preparation for deployment. The VHC-based study of the effect of women's hormonal phase on the occurrence of adverse events is likely to prove more complex than is suggested by the proposal and is considered a low priority by the committee.

The committee is pleased to see that CDC has begun to give attention to DMSS as a resource for generating and testing hypotheses concerning adverse events that might be associated with receipt of AVA.

The committee is concerned, however, about the proposed use of data mining to screen data from the Vaccine Adverse Event Reporting System (VAERS) for hypothesis generation. VAERS is a spontaneous reporting system that is inherently incomplete and subject to often-unknown reporting biases. Therefore

the committee considers it inappropriate to apply data mining techniques to VAERS data unless those techniques are thoroughly evaluated in other, more complete data sets and are shown to be effective even in the face of the kinds of biases inherent in the VAERS data. It might be possible to conduct such validation studies using DMSS data. In addition, the availability of data from both DMSS and VAERS on health outcomes following exposure to AVA provides an unprecedented opportunity to use associations that might be found in DMSS in subsequent efforts to validate the use of data mining in VAERS.

Resources for generating and testing hypotheses about adverse events and the anthrax vaccine might be better expended in the effort to use data from DMSS to their fullest potential. The committee is concerned that despite movement toward collaboration between CDC and the Department of Defense (DoD) to permit work with the DMSS databases, as of February 2002 these studies were still not receiving the appropriate attention, priority, and funding. Hypothesis testing with DMSS should be one of CDC's highest priorities, but the research plan does not reflect that.

Finally, the committee believes the proposed study of the possible role of aluminum hydroxide in adverse events would be difficult to conduct and is not of sufficient priority to pursue as part of the CDC anthrax vaccine research program.

Acceptability

Investigation of the acceptability of the anthrax vaccine was not directly specified in the congressional mandate to CDC; however, the committee recognizes the potential importance of acceptability issues to the overall success of any vaccination program. The committee found that the planned study of knowledge, attitudes, and beliefs (KABs) regarding the anthrax vaccine among members of the military was unnecessary in its proposed form. However, information about attitudes in groups that are likely to be immunized can be useful in guiding the development of interventions intended to address concerns about the anthrax vaccine. Thus, the committee recommended against exhaustively detailing the current level of concern among various categories of service members. Instead, relevant information could be gathered using focus groups and smaller surveys and then usefully applied to the development, refinement, and evaluation of the interventions.

The committee also felt that the separate survey of health care providers could be of greater value if the focus were broadened from providers' KABs about VAERS and AVA to their KABs about immunization and adverse events more generally. The committee advises including not only health care providers who administer vaccines, but also those who might see patients with concerns about adverse events. Thus while the study as proposed is considered of low priority, it could make a more important contribution to the research effort if modifications were made.

Research Gaps

In its review of the studies proposed by CDC, the committee identified gaps in the research plan. These needed studies are noted in Chapters 4, 5, and 6; in the text above; and in Table 7-2.

The committee feels that the clearest gap in the research plan as mandated by Congress is the absence of passive protection studies—studies to determine the amount of human antibody against protective antigen needed to protect rhesus monkeys from aerosol anthrax spore challenge. Studies that evaluate the impact of different challenge doses of spores on correlates of protection are also needed. Such studies would appropriately follow determinations from passive protection studies of the appropriate level of antibody needed to provide protection at a given dose. This information may have a bearing on the possible use of immune serum globulin as a prophylactic agent after exposure to anthrax spores.

The committee also perceives a gap in the efforts to link data available from the Defense Medical Surveillance System with databases that could provide additional years of follow-up among military personnel who have received AVA. Linkages with data from sources such as the Millennium Cohort Study or the Department of Veterans Affairs health system hold the potential for evaluating whether the vaccine is associated with health effects that arise in the longer term.

TABLE 7-2 Additional Research Needs Concerning the Safety and Efficacy of the Anthrax Vaccine, Identified and Prioritized by the Committee

Committee Priority	Additional Research Needs Identified by the Committee
High	Passive protection studies in nonhuman primates (Chapter 4, p. 51)
	Studies of the effect of the size of the challenge dose on protection (Chapter 4, p. 51)
	Linkage of the Defense Medical Surveillance System and other databases for longer-term follow-up of military personnel who received AVA (Chapter 5, p. 77)
Medium	Focused, small-scale surveys of knowledge, attitudes, and beliefs regarding the anthrax vaccine among military personnel to guide the design of information programs (Chapter 6, p. 87)
	Survey of civilian and military health care providers regarding vaccination and the reporting of possible vaccine-associated adverse events (modification of a study proposed by CDC, Chapter 6, p. 89)

Another research gap is suggested by the planned studies regarding acceptability. The most pressing need in that area is for studies that can help guide the design of materials and interventions to improve the acceptability of the vaccine and the design of materials and strategies to better inform health care providers who see vaccinees about the potential adverse events associated with the licensed anthrax vaccine and with vaccines more generally.

BIOTERRORISM AND RESEARCH NEEDS

CDC's research program was mandated by Congress in 1999 and initiated before the bioterrorist use of anthrax spores in 2001. The nation's experience of civilian bioterrorism confirmed the urgency of the research that CDC has already planned, but also made clear the need for studies related to the possible use of the anthrax vaccine following exposure to anthrax spores and the use of the vaccine in the civilian population. With some additions to its research portfolio, CDC could make further contributions to understanding of the safety and efficacy of AVA as it is currently used or of new uses of AVA or a new anthrax vaccine.

In particular, the CDC research plan could benefit from the addition of studies using animal models to investigate the immunogenicity of AVA (or another anthrax vaccine) when it is administered following, rather than prior to, exposure to anthrax spores. Antibiotics are also provided in such a situation to provide protection until immunity is established in response to the vaccine. AVA was offered to postal workers and Senate staff members in late 2001 following their potential exposure to anthrax spores, and such postexposure use is a likely scenario for future civilian use of an anthrax vaccine following a bioterrorist event. Because it is not ethical to expose humans to anthrax spores for research purposes, studies of postexposure use of the anthrax vaccine must be conducted in animals, such as nonhuman primates. As noted by an earlier IOM committee, only two such studies have been carried out in nonhuman primates (Friedlander et al., 1993; Henderson et al., 1956). This research is also needed to establish the appropriate duration for antibiotic prophylaxis after vaccine administration (IOM, 2002).

Finding: Additional studies in laboratory animals of the efficacy of AVA in combination with antibiotics following inhalational exposure to anthrax spores are needed to establish an appropriate duration for antibiotic prophylaxis after vaccine administration (see IOM, 2002).

Recommendation: As part of its research plan, CDC should support studies in laboratory animals to establish an appropriate duration for antibiotic prophylaxis when administered with AVA following *B. anthracis* spore challenge.

The committee also notes that there is little information concerning the immunogenicity or adverse event profile for AVA when administered to children, the elderly, or persons with chronic illnesses. Current knowledge of the vaccine's potential adverse health effects is derived from its use by a healthy adult population. In fact, the newest data come from the vaccination of military personnel subject to deployment to areas considered to be at risk for exposure to military bioweapons. Analysis of data from DMSS suggests that on average, the recipients of AVA were healthier than the general military population (IOM, 2002).

In the materials provided to the committee, CDC gave the research questions concerning postexposure vaccine use by children and the elderly a lower priority than other topics, and no mention was made of persons with chronic illnesses as a population of special concern. The CDC materials included mention of a proposed pediatric study, but indicated that the development of a study protocol depended on the availability of funding.

While recognizing the challenges involved in conducting studies in vulnerable populations, the committee is persuaded that efforts to study the use of AVA in children, the elderly, and persons with chronic illnesses should be a high priority once the findings from the human clinical trial have established the optimal route (SQ versus IM) and number of AVA doses for young and middle-aged adults. The planning for future studies in vulnerable populations should also be flexible enough to respond to changing circumstances, including the possible availability of a newer anthrax vaccine.

Finding: The exposure of members of the civilian population to anthrax spores in the bioterrorist incidents in the fall of 2001 demonstrates the importance of determining the immunogenicity and reactogenicity of AVA or any future anthrax vaccine when used by children, the elderly, and persons with chronic illnesses.

Recommendation: Studies of the use of AVA (and any future anthrax vaccine) by children, the elderly, or persons with chronic illnesses should have a high priority once the findings from the clinical trial have established the optimal route and number of vaccine doses in young and middle-aged adults. The possible availability of newer-generation anthrax vaccines should be taken into account in planning these future studies in vulnerable populations.

The bioterrorist events of 2001 also made clear the potential need to administer an anthrax vaccine following exposure to anthrax spores. Although the congressional mandate might seem to confine CDC to studies of pre-exposure use of the current anthrax vaccine, the committee urges CDC to interpret the congressional mandate broadly to improve preparedness for the possibility of future bioterrorist events involving anthrax. The research program must be flexible enough to respond to changing circumstances using both intramural and extramural resources, and to draw fully upon the expertise in vaccine development and testing available within the National Institutes of Health and DoD as it does so.

A NEED FOR A SINGLE PROGRAM LEADER

From its review, the committee sees evidence of a need for strong overall leadership of the CDC anthrax vaccine research plan to provide management and oversight. Although the research plan responds well to the specific elements of the congressional mandate, it currently includes studies that the committee concluded should have a low priority or should not be conducted, and it omits studies that the committee considers important. In the absence of authoritative centralized senior leadership, individual projects within programs can sometimes gain a momentum of their own and become difficult to modify or stop, even if they are no longer appropriate.

Given the size of the task and the nature of the work, it is appropriate that the anthrax vaccine research program receive high-level attention and direction from the leadership at CDC. However, it does not appear that it has. The interim report from this committee noted a concern that CDC had not described a comprehensive plan explaining how the array of projects it was planning fit the overall goals for the research program (IOM, 2001). Following CDC's final presentations to the committee in January 2002, the committee still did not have an understanding of the guiding plan for the research program. As a result, the committee requested that CDC provide a comprehensive written description of the research plan as of February 2002. The committee also requested a listing of the critical research questions relating to anthrax vaccine safety and efficacy, with an indication as to which studies were addressing these questions, what priority was assigned to the studies, and where research gaps remained.

After reviewing these materials, the committee concluded that despite evident hard work from the two units involved in developing and improving the proposals and protocols for the individual studies that make up the research program, there still does not appear to be a comprehensive plan guiding the continued overall development of the research program. The description of the research plan provided to the committee was developed only after repeated requests, and it did not provide a compelling rationale for the array of studies or justify CDC's prioritizations of the studies. Rather than constituting a coherent research plan, the work planned by CDC falls into two groups of studies drawing on a single ongoing source of funds but being planned and carried out by two separate organizational units within CDC. The committee concluded that centralized senior leadership would aid in the development of a single integrated plan that will make the most effective use of the total resources available to CDC.

A research program of this size and visibility can also benefit from ongoing guidance from a group of external scientific advisors who can assist in planning and setting priorities. This IOM committee has provided input for planning and prioritizing studies in the research plan, but it cannot continue and, in any case, is not well suited to providing ongoing real-time advice. CDC has responded vigorously to the IOM committee's recommendation to convene scientific advisory panels for individual studies, but there is no indication that CDC will have a future source of external advice to the research program as a whole.

The timelines for the studies that make up the research plan are also an important consideration. The timetable for the entire program must be viewed in the context of the urgent efforts to develop an alternative anthrax vaccine (Enserink and Marshall, 2002; NIH, 2002). The narrow focus and extended timelines for several of the studies might limit the usefulness of the data obtained, except to the extent that those data can inform the licensing and acceptability of new vaccines. Anticipated changes to improve the use of the current vaccine (AVA) in terms of the route of administration or the number of doses are needed as soon as possible, but will also affect plans for some of the studies. Without strong leadership to hasten some of the studies or extend their scope (e.g., the KAB studies), some of the studies may extend into irrelevancy.

Finding: The CDC anthrax safety and efficacy research program lacks clearly defined senior leadership. It also lacks an ongoing external review committee that is independent of the consultative groups for individual studies.

The committee is persuaded that effective coordination of a research program distributed across two separate organizational units of CDC requires management by a single senior CDC biomedical scientist with responsibility for the overall program. In addition to monitoring timelines and providing prioritization and strategic planning for the research program, a clearly defined leader can facilitate appropriate responses to changing circumstances and new opportunities that may arise.

Furthermore, the overall program should be overseen by an external advisory committee that will provide scientific recommendations to the program leadership on terminating studies or redirecting program resources. This group can also provide advice about the membership of the consultative groups that were convened by CDC to provide real-time input on study design. Recognizing that the administrative and procedural requirements related to such groups can be burdensome and time-consuming, the com-

mittee encourages CDC to seek the most efficient means of gaining access to ongoing expert scientific guidance.

The CDC program leader should be responsible for all aspects of the anthrax vaccine research program and have the authority to initiate, redirect, or terminate research studies, with advice from the external committee.

Recommendation: CDC should establish clearly defined senior leadership for the anthrax vaccine research program to articulate precise objectives for the research plan and to provide authority and accountability in the management of a coherent research plan. A single senior biomedical scientist should be given management authority for the entire program.

Recommendation: As soon as possible, CDC should convene an external advisory group for the overall anthrax vaccine research plan and its progress. This group should have an advisory role regarding the continuation or termination of studies that are under way, the initiation of new studies, and the direction of the entire program.

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Appendix A

Biographical Sketches

Philip S. Brachman, M.D. (*Chair*), is a professor, Department of International Health, Rollins School of Public Health (RSPH), Emory University. He joined the CDC in 1954 and worked in epidemiology and training until his retirement in 1986. He held positions in the Bureau of Epidemiology, and then the Epidemiology Program Office, which he directed from 1970 to 1981. Dr. Brachman also directed the Field Epidemiology Training Program until 1986. He subsequently joined the RSPH faculty and is primarily involved in teaching regular courses in epidemiology, biostatistics, public health surveillance, and infectious diseases in Atlanta, and 2- to 4-week short courses in the same areas in Atlanta, throughout the United States, and overseas. Dr. Brachman's current research activities include public health surveillance, nosocomial infections, and bioterrorism. He also directs the Hubert H. Humphrey Fellowship program at RSPH, a scholarship program financed by the U.S. government for foreign professionals to study and work for one year in the United States.

Adaora Alise Adimora, M.D., M.P.H., is an assistant professor of medicine and clinical assistant professor of epidemiology at the University of North Carolina School of Medicine in Chapel Hill. Her work has included efficacy trials of a herpes simplex vaccine, studies of HIV epidemiology in minority populations, and AIDS training in international settings. She also served on the FDA's Vaccines and Related Biological Products Advisory Committee.

Sandra H. Berry, M.A., is a Senior Behavioral Scientist at RAND and the Senior Director of RAND's Survey Research Group. She has 30 years of experience in survey design, measurement, operational planning, management of policy research projects, field data collection, and survey data analysis, including analysis of methodological studies. Recent work includes co-directing a study of the effect of television on adolescent sexual behavior; the Cost of Cancer Clinical Trials Study; the HIV Cost and Services Utilization Study (HCSUS), a study of HIV risks related to sexual behavior; and oversight of instrument design and data collection for HCSUS. She has directed measurement development projects in the area of low vision. She has also directed demographic and health surveys conducted in Indonesia, a community survey for the Los Angeles 2000 Committee, the Medical Outcomes Study data collection, and other health-related research.

Theodore C. Eickhoff, M.D., is Professor of Medicine in the Division of Infectious Disease, University of Colorado Health Sciences Center. He has expertise in internal medicine, infectious diseases, and epidemiology. His research interests have included nosocomial infections, the evaluation of new antimicrobial agents, and the prevention and control of influenza. He has long been interested in disease prevention

by immunization, and has been an advocate of improved immunization of adults. He has served on the Advisory Committee on Immunization Practices and the National Vaccine Advisory Committee, and was the first chair of FDA's Vaccines and Related Biological Products Advisory Committee. In addition, he has served as president of both the Infectious Disease Society of America and the American Epidemiological Society.

Patricia Ferrieri, M.D., is Professor of Laboratory Medicine and Pathology and Pediatrics at the University of Minnesota Medical School, Minneapolis, Minnesota, and Director of the Clinical Microbiology Laboratory at Fairview-University Medical Center, Minneapolis. She is also a member of the Pediatric Infectious Diseases Division. Her research interests include protein antigens of group B streptococci (GBS), pathogenesis of infection, host immunity, and animal models of bacterial infection and protection. In addition, she is involved in molecular characterization/epidemiology of GBS and other bacteria, neonatal infections, and bacterial vaccines. She is a former chairperson of the NIH Bacteriology and Mycology Study Section and the former chair of the FDA Vaccines and Related Biological Products Advisory Committee, and is knowledgeable in regulatory and licensing procedures.

Emil C. Gotschlich, M.D., is vice president for medical sciences at The Rockefeller University, where he is also R. Gwin Follis-Chevron Professor and head of the Laboratory of Bacterial Pathogenesis and Immunology. His early work led to the development of a vaccine for the prevention of group A and C meningococcal meningitis. His research has also been directed at the surface structures responsible for the pathogenicity of group B streptococci and gonococcus. Dr. Gotschlich is a fellow of the American Academy of Microbiology and is a member of both the National Academy of Sciences and the Institute of Medicine.

Maurice Hilleman, Ph.D., D.Sc., has been engaged for nearly six decades in basic and applied research in academia, government, and industry. He was formerly director and senior vice president, Merck Institute of Therapeutic Research. He is presently director of the recently formed Merck Institute for Vaccinology. As a virologist-infectious disease scientist, Dr. Hilleman has been engaged in broad-spectrum programs in basic research discovery in virology and viral immunology and in targeted research, which has yielded a large number of vaccines, including measles, mumps, rubella, varicella and combined MMR, pneumococcus, meningococcus, *H. influenzae*, hepatitis A, and hepatitis B that are now used routinely. His most recent work has focused on vaccine development, improvement, and application, with emphasis on public health policy and worldwide utilization. He engages in summary simplification of the molecular biology, pathogenesis, epidemiology, and immune prophylaxis of a number of viral infections. Other interests include AIDS, hepatitis, virus in cancer, immunology, vaccinology, public policy, and world health applications. Dr. Hilleman serves on the Committee to Review Research Proposals from Former Soviet Biological Weapons Institutes for the National Research Council Office of International Affairs and the U.S. Civilian Research and Development Foundation (CRDF), and is an elected member of both the National Academy of Sciences and the Institute of Medicine.

Dennis L. Kasper, M.D., is executive dean for academic programs, William Ellery Channing Professor of Medicine, and professor of microbiology and molecular genetics at Harvard Medical School. He also serves as director of the Channing Laboratory and as a senior physician at Brigham and Women's Hospital. With his colleagues and students, Dr. Kasper studies the molecular basis of bacterial pathogenesis, applying the resulting knowledge to enhance understanding of the interactions of bacterial surface virulence factors with host defenses. Dr. Kasper's studies focus on the molecular and chemical characterization of important bacterial virulence factors such as capsular polysaccharides, surface proteins, and toxins. The ultimate goal is to develop vaccines and immunomodulatory molecules to prevent bacterial infections

and their complications. Dr. Kasper is a fellow of the American Academy of Microbiology and the American Association for the Advancement of Science, as well as a member of the Institute of Medicine.

Michael D. Lockshin, M.D., is director of the Barbara Volcker Center for Women and Rheumatic Disease and co-director of the Mary Kirkland Center for Lupus Research at the Hospital for Special Surgery in New York City, and Professor of Medicine and Obstetrics-Gynecology at the Joan and Sanford I. Weill Medical College of Cornell University. His research interests include pregnancy and rheumatic disease, antiphospholipid antibody, and other topics related to systemic lupus erythematosus and sex differences in disease. He convened the first international Conference on Pregnancy and Rheumatic Disease and the first Conference on Gender, Biology, and Human Disease. He has served on editorial boards of numerous scientific journals and has authored more than 190 scientific papers and textbook chapters, including the health policy book, *Guarded Prognosis*. Prior to his current position, Dr. Lockshin was extramural director, then acting director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases at the National Institutes of Health. He was then senior advisor to the Director of the Clinical Center, National Institutes of Health, before returning to Cornell in 1997. Dr. Lockshin chaired the American Board of Internal Medicine Committee on Rheumatology and has chaired many committees and held national offices with the Arthritis Foundation and the American College of Rheumatology.

David Madigan, Ph.D., is professor of statistics at Rutgers University. Previously he was a faculty member at the University of Washington and at the Fred Hutchinson Cancer Research Center, both in Seattle. His work focuses on predictive modeling for large-scale multivariate data, and he has published extensively in that area. He also has research interests in clinical trials and in computational biology. He is a Fellow of the American Statistical Association.

Kathleen M. Neuzil, M.D., M.P.H., is an assistant professor of medicine in the Division of Infectious Diseases at the University of Washington School of Medicine, and a staff physician and hospital epidemiologist at the VA Puget Sound Health Care System, Seattle, Washington. Her work has included efficacy trials of influenza, respiratory syncytial virus, and varicella vaccines, as well as epidemiologic investigations of influenza and respiratory syncytial virus disease burden. Dr. Neuzil currently serves as the American College of Physicians/American Society of Internal Medicine (ACP/ASIM) liaison representative to the CDC's Advisory Committee on Immunization Practices, and is a member of the ACP/ASIM National Task Force on Adult Immunization.

N. Regina Rabinovich, M.D., M.P.H., is director, Malaria Vaccine Initiative, at the Program for Appropriate Technology in Health (PATH). Previously, she served as Chief of the Clinical and Regulatory Affairs Branch and the Clinical Studies Section of the Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health. Dr. Rabinovich currently serves on the IOM Committee on a Strategy for Minimizing the Impact of Naturally Occurring Infectious Diseases of Military Importance: Vaccine Issues in the U.S. Military. In the past she served as the NIH liaison to the Centers for Disease Control Committee on Immunization Practices and the chair of the Epidemiology Section of the American Academy of Pediatrics.

Brian L. Strom, M.D., M.P.H., is professor of biostatistics and epidemiology, professor of medicine, professor of pharmacology, director of the Center for Clinical Epidemiology & Biostatistics, and chair of the Graduate Group in Epidemiology & Biostatistics at the University of Pennsylvania School of Medicine. His clinical training and research training are in internal medicine, clinical pharmacology, and epidemiology, with a major research interest in the field of pharmacoepidemiology. He holds editorial positions on numerous journals and has authored more than 300 original papers, as well as one of the first textbooks in the field. Dr. Strom has served as president of the International Society of Pharmacoepide-

miology and as a member of the Board of Regents of the American College of Physicians. He is now on the Board of Directors for the American College of Epidemiology. He served on both the Medication Use Task Force of the Joint Commission on the Accreditation of Healthcare Organizations and the Drug Utilization Review Advisory Committee on the United States Pharmacopoeia Convention. He has been elected to the Association of American Physicians, the American Epidemiologic Society, the American Society for Clinical Investigation, and the Institute of Medicine.

Hugh H. Tilson M.D., Dr.P.H., is clinical professor of epidemiology and health policy and senior adviser to the dean at the University of North Carolina School of Public Health. Dr. Tilson is a practicing epidemiologist and outcomes researcher, with a career in preventive medicine and public health that spans more than 30 years and that includes service as a director of both state and local health departments and as vice president for worldwide epidemiology, surveillance, and policy research at GlaxoWellcome. He is the author of more than 100 papers in epidemiology, outcomes and policy research, and public health. He is a fellow of the American College of Epidemiology and is former vice-chair of the American Board of Preventive Medicine. Dr. Tilson also served as president of the American College of Preventive Medicine from 1995 to 1997 and was founding co-president of the International Society for Pharmacoepidemiology. He serves as an adviser and consultant in health outcomes, drug safety, and evidence-based health policy to regulatory and government agencies as well as pharmaceutical companies.

Appendix B

Information-Gathering Meeting Agendas

Meeting I
October 31, 2000

The Foundry Building
1055 Thomas Jefferson Street, NW
Washington, DC

Agenda

Open Session

8:00 a.m. Welcome, introductory remarks, and introductions by committee members and meeting attendees
Philip Brachman, M.D., Chairman, Committee to Review the CDC Anthrax Vaccine Safety and Efficacy Research Program

8:15 Review of charge
Philip Brachman, M.D.

8:30 Congressional staff presentation of history/motivation of appropriation
Mr. Brent Jaquet, Appropriations Fellow, Office of Congressman C.W. Bill Young

8:45 Sponsor presentation on the study charge
Jose F. Cordero, M.D., M.P.H., Assistant Surgeon General, Deputy Director, National Immunization Program, CDC

9:00 Background on anthrax
Col. Arthur M. Friedlander, M.D., U.S. Army Medical Research Institute of Infectious Diseases, DOD
LTC John D. Grabenstein, R.Ph., Ph.D., Clinical Operations, Anthrax Vaccine Immunization Program Agency

10:00 Vaccine Adverse Events Reporting System (VAERS) background
Gina Mootrey, D.O., M.P.H., Senior Research Officer, Vaccine Safety Development Activity, Epidemiology and Surveillance Division, National Immunization Program, CDC
M. Miles Braun, M.D., M.P.H., Division of Epidemiology, Office of Biostatistics & Epidemiology, Center for Biologics Evaluation and Research, FDA

10:30 Break

10:45 Background on Anthrax Vaccine Expert Committee (AVEC)
Vito Caserta, M.D., M.P.H., National Vaccine Injury Compensation Program, Health Resources and Services Administration, DHHS

11:00 Sponsor overview of CDC research program
Benjamin Schwartz, M.D., Acting Director, Epidemiology & Surveillance Division, National Immunization Program, CDC
Michael M. McNeil, M.D., M.P.H., Chief, Anthrax Vaccine Safety Activity, Epidemiology & Surveillance Division, National Immunization Program
Kristine Sheedy, Ph.D., Health Communication Specialist, Vaccine Safety Development Activity, Epidemiology & Surveillance Division, National Immunization Program
Gina Mootrey, D.O., M.P.H., Senior Research Officer, Vaccine Safety Development Activity, Epidemiology & Surveillance Division, National Immunization Program

12:15 p.m. Lunch

1:15 Sponsor overview of CDC research program, continued
Bradley A. Perkins, M.D., National Center for Infectious Diseases, CDC

2:00 Adjourn

Meeting II
February 8, 2001

The Foundry Building
1055 Thomas Jefferson Street, NW
Washington, DC

Agenda

Open Session

9:00 a.m. Welcome, introductory remarks, and introductions by committee members and meeting attendees
Philip Brachman, M.D., Chairman, Committee to Review the CDC Anthrax Vaccine Safety and Efficacy Research Program

9:15 Review of charge
Philip Brachman, M.D.

9:25	The National Center for Infectious Diseases Anthrax Vaccine Research Program: anthrax vaccine clinical trials *Bradley Perkins, M.D., Chief, Meningitis & Special Pathogens Branch, Division of Bacterial Mycotic Diseases, National Center for Infectious Diseases, CDC*
10:10	National Immunization Program opening remarks *Benjamin Schwartz, M.D., Associate Director for Science, Epidemiology & Surveillance Division, National Immunization Program, CDC*
10:20	Introduction to National Immunization Program Anthrax Vaccine Safety & Efficacy Research Program *Michael M. McNeil, M.D., M.P.H., Chief, Anthrax Vaccine Safety Activity, Epidemiology & Surveillance Division, National Immunization Program, CDC*
10:30	Break
10:45	Survey of knowledge, attitudes, and beliefs regarding the anthrax vaccine among military personnel *Deborah Gust, Ph.D., Behavioral Scientist, Vaccine Safety & Development Activity, Epidemiology & Surveillance Division, National Immunization Program, CDC*
11:15	Enhancing the reporting of vaccine adverse events: a survey of military vaccine providers *Robert Pless, M.D., Medical Epidemiologist, Vaccine Safety & Development Activity, Epidemiology & Surveillance Division, National Immunization Program, CDC*
11:45	Working lunch
12:45 p.m.	Data mining in Vaccine Adverse Event Report System *Betsy Cadwell, M.S.P.H., Mathematical Statistician, Data Management Division, National Immunization Program, CDC*
1:15	Assessing the safety of anthrax vaccine: a meta-analysis *Betsy Cadwell, M.S.P.H.*
2:00	Adjourn

Meeting III
April 18–19, 2001

The Cecil and Ida Green Building
2001 Wisconsin Avenue, NW
Washington, DC

Agenda

Wednesday, April 18

Open Session

10:30 a.m. Oral statements
MS (ret) Thomas Starkweather
Mr. Sonnie Bates
Col. (ret) Redmond Handy, National Organization of Americans Battling Unnecessary Servicemember Endangerment (NO ABUSE)
Ms. Nancy Rugo
Capt. John Buck, M.D.
Major Jon Irelan
Capt. Jean Tanner
Technical Sergeant Jeffrey Moore

Discussion

12:30 p.m. Adjourn

Thursday, April 19

Open Session

8:00 a.m. Welcome, introductory remarks, review of charge, and call to order
Philip Brachman, M.D., Chairman

8:10 National Center for Infectious Diseases anthrax vaccine research program
Bradley Perkins, M.D., Chief, Meningitis & Special Pathogens Branch, Division of Bacterial Mycotic Diseases, National Center for Infectious Diseases, CDC

8:15 Update on human clinical trial
Nina Marano, D.V.M., M.P.H., Medical Epidemiologist, Meningitis & Special Pathogens Branch, Division of Bacterial Mycotic Diseases, National Center for Infectious Diseases, CDC

8:40 Nonhuman primate studies
David Ashford, D.V.M., M.P.H., D.Sc., Medical Epidemiologist, Meningitis & Special Pathogens Branch, Division of Bacterial Mycotic Diseases, National Center for Infectious Diseases, CDC

9:05 Primary study points—measurement of anti-PA antibody
Conrad Quinn, Ph.D., Chief, Microbial Pathogenesis and Immune Response Laboratory, Meningitis & Special Pathogens Branch, Division of Bacterial Mycotic Diseases, National Center for Infectious Diseases, CDC

10:25 Break

10:40 Sub-study: human leukocyte antigen (HLA)
Robert Jacobson

11:05 Progesterone
Laurie Kamimoto, M.D., National Immunization Program, CDC

11:25 SF-36 health survey
Stacey Martin, M.S., National Immunization Program, CDC

11:45 Lunch

12:30 p.m. Adjourn

Meeting IV
July 2, 2001

The Foundry Building
1055 Thomas Jefferson St., NW
Washington, DC

Agenda

Open Session

10:00 a.m. Call to order, introductions

10:15 Introduction and overview of CDC anthrax vaccine program
Dixie Snider, M.D., M.P.H., Associate Director for Science, CDC

10:30 Definition of safety and acceptability goals/components of CDC anthrax vaccine program and relevance of activities associated with these goals/components
Ben Schwartz, M.D., Associate Director for Science, Epidemiology and Surveillance Division, National Immunization Program, CDC
Ramses Sadek, Ph.D., Statistician, Data Management Division, National Immunization Program, CDC
Michael McNeil, M.D., M.P.H., Chief, Anthrax Vaccine Safety Activity, Epidemiology and Surveillance Division, National Immunization Program, CDC
Randy Louchart, R.N., M.P.H., Deputy Chief, Anthrax Vaccine Safety Activity, Epidemiology and Surveillance Division, National Immunization Program, CDC

12:00 p.m. Lunch Break

1:00 Definition of efficacy goal/component of CDC anthrax vaccine program, relevance of activities associated with this goal/component
Bradley Perkins, M.D., Chief, Meningitis & Special Pathogens Branch, Division of Bacterial Mycotic Diseases, National Center for Infectious Diseases, CDC

2:15 Comments, questions, and answers
Discussion with the committee members

3:00 Adjourn

Meeting V
January 7, 2002

The Foundry Building
1055 Thomas Jefferson St., NW
Washington, DC

Agenda

Open Session

9:00 a.m. Call to order, introductions
Philip Brachman, M.D., Chairman, Committee to Review the CDC Anthrax Vaccine Safety and Efficacy Research Program

9:15 Introductory presentation—National Immunization Program anthrax vaccine safety activities above & beyond research
- Pre- and post-exposure investigational new drug (IND) use of AVA
- The Vaccine Healthcare Center (VHC) Network partnership with DoD

Randy Louchart, R.N., M.P.H., Deputy Chief, Anthrax Vaccine Safety Activity, Epidemiology and Surveillance Division, National Immunization Program, CDC

Addressing IOM Concerns and Input from External Expert Panels

9:45 Research priorities and the study of long-term health effects of AVA
Michael McNeil, M.D., M.P.H., Chief, Anthrax Vaccine Safety Activity, Epidemiology and Surveillance Division, National Immunization Program, CDC

10:45 Survey of military personnel about their knowledge, attitudes, and beliefs concerning AVA
Deborah Gust, Ph.D., Behavioral Scientist, Vaccine Safety & Development Activity, Epidemiology & Surveillance Division, National Immunization Program, CDC

11:15 Use of DMSS to test AVA adverse events hypotheses
Ben Schwartz, M.D., Associate Director for Science, Epidemiology and Surveillance Division, National Immunization Program, CDC

11:45 Other AVA safety research activities and collaborations—questions and comments
National Immunization Program staff

12:00 p.m. Lunch break

1:00 Overview of efficacy component of CDC anthrax vaccine program
Bradley Perkins, M.D., Chief, Meningitis & Special Pathogens Branch, Division of Bacterial Mycotic Diseases, National Center for Infectious Diseases, CDC

1:30 Update on human study
Nina Marano, D.V.M., M.P.H., Medical Epidemiologist, Meningitis & Special Pathogens Branch, Division of Bacterial Mycotic Diseases, National Center for Infectious Diseases, CDC

2:15 Update on nonhuman primate study
Jairam Lingappa, M.D., Ph.D., Medical Epidemiologist, Meningitis & Special Pathogens Branch, Division of Bacterial Mycotic Diseases, National Center for Infectious Diseases, CDC
Dave Ashford, D.V.M., M.P.H., D.Sc., Medical Epidemiologist, Meningitis & Special Pathogens Branch, Division of Bacterial Mycotic Diseases, National Center for Infectious Diseases, CDC

3:00 Break

3:15 Update on correlates of protection study
Conrad Quinn, Ph.D., Medical Epidemiologist, Meningitis & Special Pathogens Branch, Division of Bacterial Mycotic Diseases, National Center for Infectious Diseases, CDC

4:00 Committee members' discussion: comments, questions, and answers

5:00 Adjourn

Appendix C

Anthrax Vaccine Safety & Efficacy Research Plan

Centers for Disease Control and Prevention (CDC)
Department of Health and Human Services

February 21, 2002

Preface

The *CDC Anthrax Vaccine Safety & Efficacy Research Plan* (The Plan) outlines studies and activities developed by CDC to address recent concerns that have been raised about the efficacy, safety, and to some extent, the acceptability of Anthrax Vaccine Adsorbed (AVA). The development and implementation of this plan is a direct response to U.S. House/Senate Conference Appropriations Language for FY00[1] and FY01.[2] The Plan describes how CDC and its collaborators, including National Institutes of Health (NIH), Department of Defense (DoD), academic research centers, nongovernmental organizations, and private sector research organizations are responding to the Congressional charge to evaluate and improve the safety and efficacy of AVA. In one major component of this research, CDC's National Center for Infectious Diseases (NCID) and National Immunization Program (NIP) are collaborating on an AVA clinical trial due to begin enrollment in March 2002. The interim results of data collected through subjects' first 7 months of the study will be presented to the FDA for consideration of changing the route of AVA administration from SQ to IM, and elimination of the 2-week vaccine dose. At the end of the study, the entire results will be submitted to FDA for consideration of elimination of additional doses from the licensed AVA schedule. At that time, CDC will also supplement these data with results from parallel non-human primate challenge studies and additional research on immunologic correlates of protection. The CDC investigators will also evaluate the occurrence of local adverse events following AVA administration and the effect of selected risk factors, including gender on vaccine safety. CDC also is coordinating several activities to evaluate and improve adverse event reporting, evaluation, and management. As part of this activity, CDC and DoD are establishing a network of Vaccine Healthcare Centers (VHCs) of excellence within the military that will serve as a platform from which to conduct AVA safety research studies to enhance AVA's safety, efficacy and acceptability. The DoD role is to focus on the clinical management and follow-up of service personnel with vaccine associated adverse events and the CDC role is to evaluate the VHC network's impact, assess interventions and conduct vaccine safety-related research through these centers. This *CDC Anthrax Vaccine Safety & Efficacy Research Plan* proposes in greater detail several AVA research studies and activities that address the U.S. Congressional mandate to investigate the safety, efficacy and acceptability of AVA among military and civilian populations.

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[1] The FY2000 House/Senate Conference Appropriations Language specified that the funds be used to address "1) the risk factors for anthrax vaccine adverse events, including differences in rates of adverse events between men and women; 2) determining immunological correlates of protection and documenting anthrax vaccine efficacy; and 3) optimizing the anthrax vaccination schedule and administration to assure efficacy while minimizing the number of doses required and the occurrence of adverse events."

[2] The FY 2001 House/Senate Conference Appropriations Language states "Regarding the anthrax vaccine study, the conferees understand that clinical studies will be greatly facilitated by the establishment of the vaccine healthcare network, with the first site located at Walter Reed Army Medical Center."

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I. Introduction

The terrorist events of September 11, 2001 and the subsequent releases of *B. anthracis* spores in Florida, New York City, and Washington, D.C. have magnified the importance of the CDC anthrax vaccine safety and efficacy research agenda. In 1998, concerns about bioweapons led Secretary of Defense William S. Cohen to initiate a controversial program to immunize all U.S. military personnel against inhalational anthrax. In recent years, questions have been raised by members of the military, the scientific community, and Congress about Anthrax Vaccine Adsorbed's (AVA) effectiveness, reactogenicity, and possible association with long-term sequelae such as infertility, Chronic Fatigue Syndrome, and Gulf War Illnesses.

This document outlines studies and activities developed by CDC to evaluate the efficacy and safety of AVA, as requested in U.S. House/Senate Conference Appropriations Language for FY00 and FY01. In particular, it describes how CDC and its collaborators including NIH, DoD, academic research centers, and nongovernmental organizations will conduct a range of investigations to evaluate vaccine immunogenicity and correlates of protection; assess alternate vaccination schedules and routes of administration to enhance vaccine safety; and enhance reporting of adverse events after vaccination. In addition to evaluating the efficacy and short and long-term safety of AVA, CDC and its partners will use a variety of approaches to improve the acceptance of AVA amongst military personnel.

The implementation of the *CDC Anthrax Vaccine Safety & Efficacy Research Plan* will provide scientific benefits for researchers in several disciplines e.g., the identification of measurable markers of protective immunity to anthrax infection will facilitate ongoing efforts by DoD, NIH, and others to design and validate a new generation of technologically advanced vaccines that will be more effective, less reactogenic, and easier to administer than AVA.

II. Background

The bacterium *Bacillus anthracis* (anthrax) is a "Category A" biologic agent,[3] and, as the U.S. has already witnessed, a potential weapon of choice for both terrorists and rogue nations. It is relatively easy to obtain, grow, store and disseminate, and the inhalational form is nearly always fatal if untreated. During the 1980s, anthrax spores were engineered for mass dissemination at bioweapons factories in at least two nations: Iraq[4] and the former Soviet Union[4]. In 1991, concerned that weaponized anthrax might be deployed by Iraq, DoD vaccinated 150,000 troops serving in the Persian Gulf, using AVA, the only FDA-licensed human anthrax vaccine. In the years after the Gulf War, DoD continued to use AVA to immunize selected military personnel to ensure their readiness for immediate worldwide deployment. In 1998, DoD established the Anthrax Vaccine Immunization Program (AVIP), whose

[3] http://www.bt.cdc.gov/Agent/Agentlist.asp

[4] http://www.anthrax.osd.mil/Flash_interface/default.html

goal is to immunize all 2.4 million active duty and reservist military personnel.

History of the Vaccine:

AVA was developed during the 1950s as a specialized vaccine to protect mill workers, livestock handlers, veterinarians, and others at risk for cutaneous anthrax through contact with anthrax-infected animals or with contaminated animal products. It consists of the noninfectious filtrate from the culture of a heat-attenuated strain of *B anthracis* adsorbed to aluminum hydroxide adjuvant. AVA is poorly suited for mass immunization, because it requires a priming series of 6 subcutaneous injections (at 0, 2, and 4 weeks, and 6, 12, and 18 months), plus annual boosters. Moreover, subcutaneous administration of the vaccine (as well as the large number of injections) may increase the incidence of short-term side effects such as pain and swelling at the site of injection.

FDA licensed AVA in 1970.[5] Evidence for its efficacy is based on data from both human and animal models. A human clinical trial of AVA was conducted from 1955 to 1959, using a slightly different formulation than the one used in the1990s.[6] The subjects were New Hampshire mill workers who processed goat hair from animals raised in anthrax-endemic areas. Several months after the trial began, there was an outbreak of inhalational anthrax in the study population, providing an unexpected opportunity to investigate AVA's ability to provide protection against inhalational as well as cutaneous infection. The researchers documented a statistically significant reduction in the incidence of anthrax among the vaccinated group (3 cutaneous cases), as compared to the control group (18 cutaneous and 5 inhalational cases). In addition, four different AVA efficacy studies conducted in nonhuman primates indicated that the vaccine provides protection against challenge with aerosolized anthrax spores.[7, 8, 9, 10]

Animal studies suggest that AVA's efficacy is based on a protective immune response to a protein called Protective Antigen (PA).[11] The nature of that response, however, is poorly understood. PA is one of three *Bacillus anthracis* proteins that combine to produce two highly dangerous exotoxins, one that causes cardiovascular collapse and the other causes pulmonary edema. The heat-attenuation process used to produce AVA apparently denatures the portions of PA that contribute to toxin

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[5] Department of Health Education and Welfare. Investigational New Drug Application for AVA DBS-IND 180. Washington DC: Centers for Disease Control and Prevention; 1966.

[6] Brachman P, Gold H, Plotkin SA, Fekety FR, Werrin M, Ingraham NR. Field evaluation of a human anthrax vaccine. *Am J Public Health*. 1962;52:632-645.

[7] Turnbull PC, Broster MG, Carman JA, Manchee RJ, Melling J. Development of antibodies to protective antigen and lethal factor components of anthrax toxin in humans and guinea pigs and their relevance to protective immunity. *Infect Immun*. 1986;52:356-63.

[8] Ivins BE, Fellows PF, Pitt MLM, et al. Efficacy of a standard human anthrax vaccine against *Bacillus anthracis* aerosol spore challenge in rhesus monkeys. *Salisbury Medical Journal Suppl*. 1995;87:125-126.

[9] Pitt MLM, Ivins BE, Estep JE, Farchaus J, Friedlander AM. Comparison of the efficacy of purified protective antigen and MDPH [AVA] to protect non-human primates from inhalation anthr. *Salisbury Medical Journal Suppl*. 1995;87:130.

[10] Wright GG, Green TW, Kanode J, R.G. Studies on immunity in anthrax, V: Immunizing activity of alum-precipitated protective antigen. *Journal of Immunology*. 1954;73:387-391.

[11] Reuveny S, White MD, Adar YY, et al. Search for correlates of protective immunity conferred by anthrax vaccine. *Infect Immun*. 2001;69:2888-2893.

formation and cell death, while preserving the portions that elicit protective immune responses.

Current use of AVA:

AVA continues to be recommended by AVIP, for administration to military personnel serving in threat areas. However, because of limited current vaccine supply, the implementation of this policy has been limited. In addition, the Advisory Committee on Immunization Practices (ACIP), with CDC concurrence, has recently issued supplemental recommendations for the prevention of anthrax (unpublished ACIP). The supplemental recommendations reaffirm the principle of pre-exposure use of AVA based on a calculable risk assessment.[12] In the current situation of limited AVA availability, ACIP recommends that AVA be prioritized for pre-exposure vaccination of groups with high risk of repeated exposures to *B. anthracis* spores. At present, these groups include laboratory personnel handling environmental specimens (especially powders) and performing confirmatory testing for *B. anthracis* in Level B and C laboratories, and those individuals involved in environmental *B. anthracis* clean-up at multiple contaminated sites in succession. Factors increasing risk in Level B and C laboratories include the type of specimens handled (powders presenting the highest risk) and the volume of specimens handled that are positive for *B. anthracis*. In addition, in December 2001, CDC received approval from FDA to implement emergency post-exposure prophylaxis using vaccine and antibiotics for individuals exposed to B. anthracis spores through letters sent through the U.S. mail system.

Although DoD has rights to the current supply of AVA, which was produced through a DoD contract with the BioPort Corporation, emergency workers and first responders in the civilian community have expressed interest in the anthrax vaccine, an interest that is likely to grow in view of the terrorist attacks on New York City and Washington, D.C. and the releases of *B. anthracis* in Florida, New York City, and Washington D.C. Given the current circumstances, information about the efficacy and safety of AVA is extremely important to both military personnel and civilians.

III. List of Approved and Proposed Research Studies with Prioritization

Each of CDC's approved and proposed AVA research studies are listed below. Included in the list are the studies' prioritization and an explanation for the basis of their prioritization. An integrated timeline of all CDC's AVA research studies is included in Section 2 of the binder and a table that outlines the critical AVA safety and efficacy research questions that are addressed by each study is included in Section 3 of the binder.

Study 1. AVA Human Reactogenicity and Immunogenicity Trial to Address Change in Route of Administration and Dose Reduction (See Section 6 in the binder for study summary)

[12] Ashford D.A., Rotz L.D., Perkins B.A. Use of anthrax vaccine in the United States: recommendations of the Advisory Committee on Immunization Practice (ACIP). MMWR 2000;49 (no. RR-15).

Priority: Level 1
Basis: The human clinical trial is expected to serve as the principal scientific basis for decisions regarding changes in route of vaccine administration and reduction in number of doses in the vaccination series. In combination with the other studies, this trial will provide new understanding about anthrax pathogenesis and immunologic correlates for protection against inhalational anthrax in humans. This work is expected to serve as the scientific foundation for development and licensing of the next generation of anthrax vaccines.

Study 2. Non-human Primate Vaccine Dose Ranging, Immunogenicity and Challenge Trial (See Section 7 in the binder for study summary)

Priority: Level 1
Basis: The Food and Drug Administration (FDA) supports use of animal studies to evaluate AVA efficacy in protecting against aerosol *B. anthracis* spore challenge; data from these studies will be used to support conclusions from the human clinical study. The non-human primate studies were therefore planned with the primary objective being use of anthrax aerosol challenge of AVA vaccinated animals to generate data about protection of animals at various points in the immunization process. This data will be used as evidence to support the objective of dose reduction in the licensed AVA schedule for humans. The immune response data collected from immunizing and challenging animals will be used to identify correlates of protection induced by AVA vaccination.

Study 3. Correlates of Protection Study (See Section 8 in the binder for study summary)

Priority: Level 1
Basis: Despite the extensive research on anthrax pathogenesis and vaccines over the past 20 years the existence of a correlation between survival from virulent anthrax challenge and a defined immune response to anthrax vaccine components, and to PA in particular, remains unresolved. In the case of human vaccinees, where clinical trials of efficacy are untenable, it is clearly expedient to have an accessible and reliable surrogate marker of immune protection. The overall purpose of this study is to determine in NHPs an immunologic correlate of protection against anthrax and correlate these data with information from the human clinical trial to test the hypothesis that

> *'One or more measurable immunological markers of protection can be identified in a NHP model of inhalation infection with B. anthracis and that one or more of these measurable markers are identifiable or present in AVA-vaccinated humans.'*

The objective of the Immune Correlates of Protection studies is to establish an immunologic

marker that endorses the human clinical trial endpoint, confirms human vaccinee protection, identifies when protection is achieved and determines how long protection lasts.

Study 4. National Survey of Knowledge, Attitudes, and Beliefs Regarding the Anthrax Vaccine Among Military Personnel (See Section 9 in the binder for study summary)

Priority: Level 1
Basis: This is the only nationally representative survey that is designed to measure the KAB's and the level of concern regarding AVA. This study will yield the most valid estimate of acceptability of AVA among military personnel. A contract has been established with RTI and the draft protocol has been submitted for regulatory approval.

Study 5. Survey of Civilian and Military Healthcare Providers regarding the Anthrax Vaccine and the Reporting of Possible Vaccine-Associated Adverse Events (See Section 10 in the binder for study summary)

Priority: Level 1
Basis: This is the only nationally representative survey to obtain data on the knowledge and awareness of VAERS, and the attitudes and practices of both military and civilian healthcare providers regarding the reporting of adverse events following AVA immunization. A contract has been established with RTI and a draft protocol is being developed.

Study 6. Study Protocol of Long-term Adverse Effects from Anthrax Vaccination Among Civilian Workers (See Section 11 in the binder for study summary)

Priority: Level 1
Basis: This will be the first long-term (>10 years) health effects study of a nonmilitary population previously vaccinated with AVA. An interagency agreement with the Social Security Administration has been established and a draft protocol has been completed and internally reviewed.

Study 7. The VHC Platform for AVA Related Research (See Section 12b in the binder for study summary)

a. Effects of Route of Administration on the Occurrence of Local Adverse Events Following Immunization with AVA

b. Effects of Hormonal Phase in the Female Population on the Occurrence of Adverse Events Following Immunization with AVA

c. Comparative Evaluation of the Effect of AVA on Health Related Quality of Life

Priority: Level 1
Basis: The research questions being addressed in this series of VHC proposed studies are of primary importance and mandated in the congressional language. A draft protocol has been completed and is being reviewed by DoD for their comment and support. The lead and first regional VHC held their open house on Sept. 6, 2001.

Study 8. Enhanced Signal Detection and Hypothesis Testing for Adverse Events Following Anthrax Vaccination & MOU Between AVSA/NIP and AMSA/DoD (See Section 13 in the binder for study summary)

Priority: Level 1
Basis: In 2000, CDC received congressional funding to perform studies to evaluate and enhance the safety and efficacy of anthrax vaccination. A key part of this program is to improve surveillance to detect adverse events and to investigate those events for association with vaccination. Collaboration with AMSA, and the use of DMSS for hypothesis testing studies is an important component in a system that will allow detection and evaluation of AVA AEs, fulfilling the congressional mandate to CDC. An MOU has been drafted and has been submitted for DoD review, comment and approval.

Study 9. Proposed Evaluation of the Anthrax Vaccine and Antibiotics Availability Program (Draft protocol available on request)

Priority: Level 2
Basis: In recent years, there has been increasing public concern about vaccine safety. Subsequently, there is a growing need to better understand information needs and public perceptions of vaccine risks and benefits in order to improve vaccine risk communication efforts. The availability of AVA to persons of varying races and socio-economic backgrounds who were exposed to inhalation anthrax will allow us to gain insight into vaccination decision-making in a context in which disease and vaccination risks are uncertain and strong recommendations by government agencies are absent. Information gained through this study will help guide future educational efforts associated with vaccination programs and to frame educational materials. A draft protocol has been completed.

Study 10. Proposed Pediatric Study – Evaluation of Post-exposure Regimens, Using a Dose Escalation Approach (Protocol to be developed depending on availability of funding.)

Priority: Level 1

Basis: The importance of this proposed study is demonstrated by the recent anthrax terrorist events. AVA is currently licensed only for use in adults. The results of this proposed evaluation would enable modified use for children in a post-exposure setting.

Study 11. Possible Role of Aluminum Hydroxide Adjuvant in AVA-Associated Adverse Events, Potential Areas for Future Research (See Section 14 in the binder for proposed study summary)

Priority: Level 2
Basis: AVA contains greater amounts of aluminum hydroxide adjuvant than other vaccines. There are no human studies that evaluate the clearance of aluminum hydroxide adjuvant from the site of injection. This adjuvant may have a role in the development of local adverse events. This study is currently in development.

IV. Objectives

The *CDC Anthrax Vaccine Safety & Efficacy Research Plan* focuses on three main objectives:

1. Efficacy

Rationale:

Because AVA's efficacy in providing protection against inhalational anthrax cannot be ethically evaluated in human subjects, the efficacy studies will involve concurrent trials in humans and non-human primates. The animal studies will include a dose-ranging study whose aim is to induce a graded series of humoral and cell-mediated immune responses in animals vaccinated with different dilutions of AVA, using 3 priming shots of each dilution in each trial group. Immune responses will be compared in vaccinated animals that survive or succumb to infection upon challenge with live, inhaled anthrax spores. The goal is to identify one or more immunological markers of protection in the non-human primates that can be measured in AVA-vaccinated humans and to use these data to support a labeling change for AVA.

Regulatory considerations:

The efficacy data, along with safety data, will be used to support an application to FDA to change the labeling of AVA to allow administration by intramuscular injection and a reduction in the number of priming shots. According to a rule proposed by FDA on October 5, 1999,[13] it is permissible to substitute animal data along with human safety and immunogenicity data in situations in which efficacy studies in humans are not ethically permissible.

[13] Federal Register 64:53960-70, 1999. Evidence needed to demonstrate efficacy of new drugs for use against lethal or permanently disabling toxic substances when efficacy studies in humans ethically cannot be conducted. URL: http://www.fda.gov/cber/rules.htm

Summary of Objectives for Efficacy

Human clinical trials:

A. Assess AVA efficacy in humans immunized with AVA [**Study 1**], by measuring immune responses identified as protective in efficacy objective B. Immune markers of protection will be evaluated under these conditions:

- When the number of priming shots is 3, 4, 5, or 6 and the vaccine is administered by intramuscular injection, and with boosters at varying intervals; and
- When the number of priming shots is 6 and the vaccine is administered by subcutaneous injection with an annual booster (standard conditions)

Non-human primate studies:

B. Assess AVA efficacy in animals immunized with serial dilutions of AVA and challenged with live, inhaled anthrax spores [**Studies 2 and 3]**

C. Use blood samples from the subjects in the clinical trial [**Study 1**] and in animal studies [**Studies 2 and 3**] to identify immune correlates of protection and validate laboratory assays to measure them [**Study 4**].

2. Safety

Rationale:

In 1998, a program to vaccinate all U.S. active and reservist service personnel with AVA was initiated by Secretary of Defense William S. Cohen. The program has elicited some opposition among service personnel and allegations have been made regarding the health effects associated with the vaccine including high rates of local adverse events, and possible linkage with Gulf War Illness, Chronic Fatigue Syndrome, and reproductive toxicity. These concerns led the U.S. Congress to appropriate funds for a collaborative effort by the CDC, NIH, and DoD to study the safety and efficacy of vaccines used against *B. anthracis*. Under CDC's mandate, evaluation of the potential link between AVA vaccination and adverse events (AEs) is of primary importance. CDC's safety research agenda includes the following objectives:

- To investigate potential long-term sequelae of AVA.
- To gain a better understanding about the type, frequency, and gender differences of vaccine AEs associated with AVA.
- To evaluate the completeness and accuracy of reporting of AVA AEs in the military and to develop and implement interventions to improve AVA AE reporting and surveillance.

- To assess AVA administration practices and the military immunization health care system that may impact AVA AEs, and enhance AVA delivery practices (quality assurance of AVA administration services in the military).

- To evaluate concerns that military personnel may have about AVA and improve their knowledge and understanding about the risk benefits of AVA and other vaccines.

- To provide AVA information, education, and communication resources to the civilian public and to military personnel in collaboration with DoD.

Safety studies conducted as part of the human clinical trials will help determine whether intramuscular administration and a reduction in the number of priming shots decreases the incidence of local AEs, and other short-term AVA-associated AEs. These studies will also help identify potential risk factors for AEs (e.g., gender differences).

Additional safety studies will seek to identify rare or long-term AVA-associated AEs and attempt to determine whether these events are causally linked to vaccination. These studies will employ a variety of approaches, including active surveillance of recent AVA recipients and a study of civilians who received AVA more than 10 years ago. Efforts will also be made to improve the completeness and accuracy of reporting of AVA-associated AEs to the Vaccine Adverse Reporting System (VAERS) administered jointly by CDC and FDA.

A potential area being considered for future safety research is elucidating the possible role of aluminum hydroxide adjuvant in AVA-associated AEs [**Study 11**].

Vaccine Health Center (VHC) Network:

Enhanced surveillance for and enhanced clinical management of AVA-associated AEs will be conducted at civilian-staffed Vaccine Health Centers (VHCs) established by a partnership between CDC and DoD, in accord with FY 2001 House/Senate Conference Appropriations Language.[2] Future studies conducted in collaboration with the VHCs will seek to improve prevention or clinical management of AVA-associated AEs, enhance the understanding of potential AVA-associated AEs, and study the safer use of AVA for persons who may be more prone to AVA-associated AEs.

Summary of Objectives for Safety

Human clinical trial:

A. Compare types and rates of occurrence of AEs associated with AVA vaccination when:
- The number of priming shots is 3, 4, 5, or 6 [**Study 1**]
- The route of administration is intramuscular or subcutaneous [**Study 1**]

B. Identify and evaluate possible risk factors for AEs among men and women [**Study 1**], including the hormonal status of female vaccine recipients [**Studies 1 and 7b**]

C. Evaluate the impact of AVA vaccination on health-related quality of life [**Studies 1 and 7c**], using the SF-36 Health Survey

Other safety studies:

D. Identify rare or long-term AVA-associated adverse events, through:

- Active, VHC-based surveillance for AVA-associated AEs [**Study 7**].
- A long-term follow-up study of civilian AVA vaccine recipients [**Study 6**].
- Utilizing the Defense Medical Surveillance System (DMSS), a database that links vaccination history to patient demographics and health outcomes, to conduct enhanced signal detection and hypothesis testing [**Study 8**].
- The Brighton Collaboration, a web based network of U.S. and international scientists whose goal is to develop standard case definitions for AEs, which will facilitate improved analysis of vaccine safety studies reported in the literature.

E. Determine whether particular AEs are causally linked to administration of AVA, making use of:

- Chart-review assessments of individuals with AEs reported to VAERS, conducted by the Anthrax Vaccine Expert Committee (AVEC).
- Chart review and physical assessments conducted by personnel of the VHC Network and others of military personnel who are reported to have AVA-associated AEs or who have health events that may be related to AVA.
- Retrospective case-control studies of AVA-associated AEs identified through utilization of the DMSS [see Safety Objective D and **Study 8**]

F. Improve completeness and accuracy of reporting of AVA-associated AEs to VAERS by:

- Using a "Knowledge, Attitudes, and Beliefs" (KAB) survey of military and civilian vaccine providers to identify barriers to reporting vaccine-related AEs to VAERS. **[Study 5]**
- Instituting web-based reporting to VAERS
- Through the VHC network, survey military personnel treated for AEs about their complete and accurate reporting to VAERS.

G. Collaborate with the VHC Network and other entities within DoD (i.e., AVIP and AMSA) to study, prevent, and improve the clinical management of AVA-associated AEs by:

- Assuring that approved practices for handling and administering AVA are followed by military vaccine providers (quality assurance).
- Determining whether pretreatment with corticosteroids or antihistamines can

reduce local AVA-associated AEs in persons who exhibit moderate to severe symptoms after the first or second priming dose.

- Conducting clinical evaluations and retrospective studies of individuals with rare AVA associated AEs. Identification methods for these individuals will occur through VHC Network and/or VAERS reports (including as a result of enhanced signal detection methods) [**Study 8**].
- Testing hypotheses about possible AVA-associated AEs in large, linked database such as DMSS [Safety Objective D and **Study 8**]. Retrospective chart reviews by VHC personnel and others would be conducted as part of hypothesis testing.
- Evaluating types and rates of occurrence of AEs associated with AVA vaccination.
- Monitoring and comparing the types and rates of occurrence of AVA-associated AEs before and after any changes in route and dosing regimen that is approved by FDA (this will be a continued assessment of any changes in route and dosing schedule as a result of the human clinical trial) [**Study 1**].
- Assessing possible differences in risk factors between men and women for AVA-associated AEs including the hormonal status of female vaccine recipients [**Study 7b**]. This is related to the study of differences in rates of AVA-associated AEs between men and women conducted in the AVA Clinical Trial [**Study 1**].
- Evaluating the impact of AVA vaccination on quality of life in military personnel using the SF-36 Health Survey [**Study 7c**] and comparing to similar data from civilian personnel from the Clinical Trial [**Study 1**].

3. Acceptability

Rationale:

Critics of the DoD's mandatory program for AVA vaccination have alleged that underreporting of AVA associated AEs has occurred. There also have been some well-publicized instances of service personnel who refused the immunization, some on the basis of alleged severe adverse health effects. Through the AVIP, the DoD has 1) conducted an intensive review of currently available data on the efficacy and safety of AVA including the establishment of the AVEC to review all AVA-associated VAERS reports, and contracting with a Committee of the Institute of Medicine (IOM) to review safety and efficacy of the vaccine, 2) conducted additional surveys and epidemiologic studies of service personnel receiving AVA to identify potential severe adverse health effects, and 3) established specific educational interventions including a quadfold information brochure on AVA, a hotline, a website, and other training materials and development of an expert model to identify barriers to risk communication and further direct educational efforts. However, no nationally representative survey of service personnel has been

conducted to gauge the nature and extent of their concerns about AVA and the extent of underreporting of AEs to VAERS.

Summary of Objectives for Acceptability

A. KAB surveys [**Study 4**], patient satisfaction survey, and other assessment tools will be developed and used to identify concerns about anthrax vaccination among military vaccine recipients**.** Research partners will include the DoD, the VHC Network, and the Research Triangle Institute (RTI).

B. In collaboration with AVIP, VHC Network, and others, knowledge gained from the KAB surveys and the efficacy and safety studies will be used to:

- Develop, promote, and provide training that will optimize and standardize procedures and quality assurance practices for the administration of AVA.
- Develop strategies and training materials to help improve the acceptability of AVA and military immune readiness, in general.

C. Train NIP Hotline and other CDC Hotline personnel to respond effectively to military and public questions and concerns about AVA.

D. A repeat KAB survey and other assessment tools will be used after education and training interventions to measure changes in KABs and impact of interventions.

V. Scientific Benefits

The implementation of the *CDC Anthrax Vaccine Safety & Efficacy Research Plan* will have significant future benefits beyond the immediate ones of evaluating the safety, efficacy, and acceptability of AVA. For example, the identification of the immune correlates of protection against anthrax infection, as well as the standardization of relevant immunologic assays will speed the development, laboratory evaluation, and clinical testing of the next generation of anthrax vaccines. For example, U.S Army Research Institute for Infectious Diseases (USAMRIID) and NIH/NIAID, are working to produce a vaccine that uses purified PA expressed from a cloned copy of the PA gene (the recombinant PA [rPA] vaccine). These efforts will be greatly assisted by CDC testing of the blood samples taken from participants in the planned NIH Phase 1 safety study of an rPA vaccine, using the same assays as planned for the CDC correlates of protection studies.

In light of recent terrorist events in New York City, Washington D.C., Florida and New Jersey, there has been a heightened awareness that CDC should play a major role in enhancing public health preparedness in the event of future attacks. Because of the clinical centers, data management, and laboratory infrastructure that has been developed to date, CDC is now in a position (using separate funding) to initiate studies to evaluate post-exposure AVA regimens in pediatric populations, alternative

therapeutic strategies such as immune globulin and to vaccinate civilians at high risk for exposure to anthrax under an emergency Investigational New Drug (IND) application filed in October 2001.

VI. Partnerships

The human clinical trial of AVA efficacy and safety as well as complementary animal studies [**Study 1**] was designed in partnership with NIH, DoD, and FDA. Implementation of this trial and of the other components of the *CDC Anthrax Vaccine Safety & Efficacy Research Plan* will require ongoing collaboration and technical assistance from these agencies, as well as from other partners in the public and private sectors.

National Institutes of Health:

NIH's National Institute of Allergy and Infectious Diseases (NIAID/NIH) will continue to provide expert consultation through the Interagency Scientific Working Group on Anthrax Vaccine Research, which will meet every three months by phone or in person to monitor the progress of these studies.

In addition, NIAID/NIH scientists will:

- Supply rPA and lethal factor for use in developing and standardizing immunologic assays.
- Perform plasmapheresis at the NIH Clinical Center on anthrax vaccinees from USAMRIID who donate plasma for use in testing of immunologic response.

Department of Defense:

CDC will continue to partner with DoD and expand the VHC network, which will serve as a platform from which to conduct AVA safety and acceptability research among military personnel.

DoD centers and divisions involved in the partnership thus far include:

- Walter Reed Army Medical Center (WRAMC), which will serve as the lead VHC site and first regional site.
- North Atlantic Medical Research Command (NAMRC).
- Walter Reed Army Institute of Research (WRAIR), which is one of the five sites participating in the clinical trial.
- Army Medical Surveillance Activity (AMSA), receives medical surveillance data (including data on AEs associated with vaccination) from each of the services and maintains it in the DMSS.
- USAMRIID, which will recruit anthrax vaccinees to donate plasma for use as a reference standard in developing assays that measure protective immune responses.

USAMRIID and AVIP will also participate (along with NIH/NIAID) in the Interagency Working Group on Anthrax Vaccine Research.

The Food and Drug Administration:

CDC is working with FDA to improve the completeness and accuracy of reporting to VAERS (Safety Objective F), which is jointly administered by the two agencies. Input from FDA has been essential in developing research protocols (see Appendix A) to generate data that may help support an application to change the labeling of AVA that would allow administration by intramuscular injection and fewer doses in the vaccination regimen.

Universities and medical centers:

The human clinical trial is being performed in collaboration with scientists and physicians at Emory University School of Medicine, Baylor College of Medicine, Mayo Clinic and Foundation, Walter Reed Army Institute of Research and University of Alabama at Birmingham. Additionally, Emory University Vaccine Center will also conduct correlates of protection studies.

Academic scientists also participate in:

- Expert panels that review CDC's research protocols and the NIP's research agenda for investigating the safety of AVA.
- The AVEC, a group of civilian physicians and epidemiologists convened by the Department of Health and Human Services at the request of DoD to review cases of AVA-associated AEs reported to VAERS.
- The "Brighton Collaboration" a web-based group of U.S. and international scientists whose goal is to develop standard case definitions for AEs.

Private sector organizations:

CDC's nongovernmental collaborators include individuals from:

- The RTI, a non-profit contract research organization, that has been contracted to implement the two KAB surveys among military and civilian vaccine recipients (Acceptability Objective B).
- Battelle Memorial Institute, a non-profit organization that will conduct the non-human primate challenge studies and correlates of protection studies [**Study 1**].
- The Medical Outcomes Trust, a non-profit organization that developed and validated the SF-36 Health Survey, an assessment tool that measures health status and outcomes from the patient's perspective (Safety Objective C).

VII. Expert Review and Oversight

Due to the scientific complexity of the issues involved in vaccine evaluation, as well as the increased need for transparency when addressing politically sensitive issues, CDC has arranged for oversight of all aspects of the AVA studies from recognized experts in vaccine research, medicine, microbiology, and statistics.

Institute of Medicine:

At CDC's request, the IOM has established an expert scientific panel to meet on a periodic basis to review the completeness and appropriateness of the activities described in this plan.

Expert Consultation Panels:

To date, seven issue-specific scientific panels have been convened at CDC to review the various components of the *CDC Anthrax Vaccine Safety & Efficacy Research Plan* (See Appendix A for a list of panel members). They include:

- **The Human Clinical Trial Data Safety Monitoring Board,** which met in September, 2001, and which will meet on a quarterly basis throughout the clinical trial, to review all aspects of human clinical trial design, including **Studies 1** through **3**.

- **The Laboratory Issues Panel,** which met in September, 2001, to review the laboratory assays in **Studies 1** through **3**, and which will meet on a semi-annual basis to confirm that the assays are adequate for identifying and measuring immunologic markers of immune protection in animals and humans.

- **The Statistics Panel**, which met in October, 2001, and which will meet on a semi-annual basis to consider how to perform multiple imputations of the clinical trial data set to properly account for missing data from non-compliance or loss to follow-up, and to consider how the correlates of protection data (**Study 3**) might be pooled and analyzed to make inferences about how long protection lasts, when protection is achieved and whether a reduced number of priming shots will provide adequate protection in humans.

- **The Nonhuman Studies Evaluation Panel**, which met in October 2001, and which will meet on a semi-annual basis to consider whether **Study 3** are adequately designed to help answer the question of whether AVA can protect humans from inhalational anthrax.

- **The Ad hoc Panel for Review of the National Immunization Program's Research Agenda for Investigating the Safety of AVA,** which met in October, 2001, the panel was asked to offer comments on the overall focus and design of NIP's AVA-related research agenda, and to offer recommendations on improvements and/or enhancements to the research agenda.

- **The Ad hoc Panel for Review of the National Immunization Program's KAB Survey Protocol,** which met in December, 2001, to review the research protocol for the national survey of knowledge, attitudes and beliefs regarding the anthrax vaccine among military personnel and to offer recommendations on improvements and/or enhancements to the research protocol.

- **The CDC Internal Panel to Review the Draft Protocol for a Long-term Follow up Study of Civilian Recipients of AVA**, which met October, 2001, to review the draft research protocol for evaluating the mortality experience and current functional

status of persons who were vaccinated with AVA more than 10 years ago. In addition to providing insights into the potential association of AVA with long-term AEs, the results of this study may suggest plausible areas for follow up research into the causal pathways of any long-term AEs that may be attributable to AVA. The panel made recommendations for improvements to the draft research protocol.

- **The CDC External Panel to Review the Draft Protocol for a Long -term Follow up Study of Civilian Recipients of AVA** is proposed for second quarter 2002.

The members of the scientific panels are listed in Appendix A. They represent universities, medical centers, private companies, and other nongovernmental institutions.

VIII. Anticipated Outcomes

The comprehensive research plan detailed in this document should provide the following important outcomes:

- Optimization of the AVA vaccination schedule and route of administration to ensure efficacy while minimizing the occurrence of AEs.
- Identification of the immune correlates of protection against anthrax infection.
- Documentation of the efficacy of AVA in humans.
- Elucidation of the safety profile of AVA and identification of any long-term sequelae associated with AVA.
- Identification of risk factors for AEs among men and women.
- Adoption of optimized vaccination procedures and quality assurance practices.
- Improved acceptance of AVA among military personnel and civilians.
- Standardization of immunologic assays for use in developing and validating the next generation of anthrax vaccines.

IX. Discontinued Previously Proposed Studies

Meta-Analysis Study: Difficulties involved in combining information from different studies for the purpose of determining a single index of risk in a meta-analytic frame-work are well known. The problems of combining data from anthrax studies are even more challenging because of the following

reasons: 1) the studies were conducted using different versions of vaccine over time, 2) the definitions of safety data elements were not necessarily uniform among different studies, 3) the method of data collection across different studies was not same, (passive versus active, self reported versus clinical observation and/or assessment), 4) the populations studied varied in risk of developing reactions and/or disease when exposed to anthrax antigen (factory workers versus DOD servicemen). Since it was not possible to combine data from published studies without substantially reducing the confidence that could be placed on the results from these analyses, CDC made the decision to discontinue the Meta-Analysis Study.

X. Acknowledgements

CDC acknowledges the contributions of Ms. Alexandra Levitt, as well as staff of the NCID Anthrax Vaccine Research Program (AVRP) and the NIP Anthrax Vaccine Safety Activity (AVSA) in the preparation of this document.

Appendix A. Expert Consultation Panels

Data Safety Monitoring Board
Date: Sept 28, 2001
Charge: To review all aspects of human clinical trial design, including Studies 1 through 3.
Panel Members:

Stanley Plotkin, M.D.
Aventis Pasteur

William Schaffner, M.D.
Vanderbilt University

John Sever, M.D.
National Childrens Medical Center

Lisa Jackson, M.D., M.PH.
University of Washington

Larry Moulton, Ph.D.
Johns Hopkins University

Neal Halsey, M.D.,
Johns Hopkins University

Robert Levine, M.D.
Yale University

Laboratory Issues Panel
Date: September 24-25, 2001
Charge: To review the laboratory assays in Studies 1 through 3, and confirm that they are adequate for identifying and measuring immunologic markers of immune protection in humans and animals.
Panel Members:

Timothy Hirst, Ph.D.
University of Bristol

Steve McDougal, M.D., Ph.D.
CDC

Julie Westerink, M.D.
Medical College of Ohio

Stephen Hildreth, D. Ph.
Wyeth-Lederle Vaccines

Statistics Panel
Date: October 1-2, 2001
Charge: to consider how to perform multiple imputations of the clinical trial data set to properly account for missing data from non-compliance or loss to follow-up, and to consider how the correlates of protection data (Study 3) might be pooled and analyzed to make inferences about how long protection lasts, when it is achieved and whether a reduced number of priming doses will provide adequate protection in humans.
Panel Members:

Steven Self, Ph.D.
Scharp Organization

Gregory Ridgeway, Ph.D.
Rand Corporation

Donald Rubin, Ph.D.
Harvard University

Nonhuman Studies Evaluation Panel
Date: October 4-5, 2001
Charge: To consider whether the design of the nonhuman primate studies (Study 2 and 3) is adequate to determine whether AVA will protect humans from inhalational anthrax.
Panel Members:

Porter Anderson, Ph.D.
University of Rochester Medical Center

Dr. Scott Giebink, M.D.
University of Minnesota

The Ad hoc Panel for Review of the National Immunization Program's Research Agenda for Investigating the Safety of AVA
Date: October 19, 2001
Charge: To offer comments on the overall focus and design of NIP's AVA-related research agenda, and to offer recommendations on improvements and/or enhancements to the current research agenda.
Panel Members:

Col. Denise Baken,
Office of Health Affairs, Secretary of Defense

Robert Chen, M.D., M.A.,
Chief, Vaccine Safety and Development Activity, ESD, NIP, CDC

Dennis M. Dixon, Ph.D. Chief, Bacteriology and Mycology Branch, Division of Microbiology and Infectious Diseases, NIH/NIAID

Lt. Col. John Grabenstein, Ph.D., R.Ph.
Deputy Director, Anthrax Vaccine Immunization Program, Office of the Surgeon General, US Army

Charles M. Helms, M.D., Ph.D.
Professsor of Medicine, University of Iowa Hospital and Clinics

Nina Marano, D.V.M., M.P.H.
Coordinator, Anthrax Vaccine Research Program, Meningitis and Special Pathogens Branch, NCID, CDC

Col. Bryan Martin, D.O.
Deputy Chief, Department of Allergy and Immunology, Walter Reed Army Medical Center

Lt. Col. Phillip Pittman, M.D., M.P.H.
Senior Scientist, USAMRIID

The CDC Internal Panel to Review the Draft Protocol for a Long-term Follow up Study of Civilian Recipients of AVA
Date: October 4, 2001
Charge: To review the draft research protocol for evaluating the mortality experience and current functional status of persons who were vaccinated with AVA more than 10 years ago. In addition to

providing insights into the potential association of AVA with long-term adverse effects, the results of this study may suggest plausible areas for follow up research into the causal pathways of any long-term adverse events that may be attributable to receipt of AVA. The panel also made recommendations for improvements and/or enhancements to the draft research protocol.

Panel Members:

Bill Thompson, Ph.D.
Biostatistician, VSDA, ESD, NIP, CDC, Atlanta

Colleen Boyle
Acting Assoc for SPP
NCBDDD

Teresa M. Schnorr, Ph.D
Assistant Chief,
Industry Wide Studies Branch
Div Surveillance, Hazard Evaluations, and Field Studies (DSHEFS)
NIOSH, CDC, Cincinnati

Matthew Zack, M.D.
Medical Epidemiologist
Health Care and Aging Studies Branch
DACH, NCCDPHP, CDC

Alison Mawle, M.D.
Research Biologist
NCID, OD, CDC, Atlanta

Ralf Coates, Ph.D.
Assoc Dir for Science
NCCDPHP, CDC, Atlanta

Drue Barrett, Ph.D., M.S., M.A.
Medical Epidemiologist
DEHHE,OD
NCEH, CDC, Atlanta

The Ad hoc Panel for Review of the National Immunization Program's KAB Survey Protocol

Date: December 4, 2001

Charge: To review the draft study protocol for the national survey of knowledge, attitudes and beliefs (KABs) regarding the anthrax vaccine among military personnel and to offer recommendations on improvements and/or enhancements. In particular recommendations concerning the soundness of study design, and strategies to ensure the methods proposed answer the aims of the KAB survey in each of

the following areas:

- Does the study design appear feasible?
- Will the methods proposed answer the aims outlined for the KAB study?
- Are the sampling strategies adequate and effective?
- Is the longitudinal component well planned?
- Are the components of cognitive testing, social desirability, and psychometric analysis sound?

Panel Members:

Col. Gary D. Gackstetter, D.V.M., M.P.H., Ph.D.
Assistant Professor and Deputy Director
Uniformed Services University of the Health Sciences

Donald Hedeker, Ph.D.
Professor of Biostatistics, School of Public Health
University of Illinois at Chicago

Michael Puma, Ph.D.
Principal Research Associate
The Urban Institute, Washington DC

Michael Schwerin, Ph.D.
Navy Personnel Research Studies & Technology Dept
Institute for Organizational Assessment, Millington TN

Paul Levy, Sc.D.
Professor of Biostatistics & Epidemiology
School of Public Health
University of Illinois at Chicago

Appendix D

Food and Drug Administration Final Rule: New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible

d.6. Silicon carbide;
d.7. Tantalum or tantalum alloys;
d.8. Titanium or titanium alloys;
d.9. Titanium carbide; *or*
d.10. Zirconium or zirconium alloys.
e. Distillation or absorption columns of internal diameter greater than 0.1 m, and liquid distributors, vapor distributors or liquid collectors designed for such distillation or absorption columns, where all surfaces that come in direct contact with the chemical(s) being processed are made from any of the following materials:
e.1. Alloys with more than 25% nickel and 20% chromium by weight;
e.2. Fluoropolymers;
e.3. Glass (including vitrified or enamelled coatings or glass lining);
e.4. Graphite or carbon-graphite;
e.5. Nickel or alloys with more than 40% nickel by weight;
e.6. Tantalum or tantalum alloys;
e.7. Titanium or titanium alloys; *or*
e.8. Zirconium or zirconium alloys.
f. Remotely operated filling equipment in which all surfaces that come in direct contact with the chemical(s) being processed are made from any of the following materials:
f.1. Alloys with more than 25% nickel and 20% chromium by weight; *or*
f.2. Nickel or alloys with more than 40% nickel by weight.
g. Valves with nominal sizes greater than 1.0 cm (3/8 in.), in which all surfaces that come in direct contact with the chemical(s) being processed or contained are made from any of the following materials:
g.1. Nickel or alloys with more than 40% nickel by weight;
g.2. Alloys with more than 25% nickel and 20% chromium by weight;
g.3. Fluoropolymers;
g.4. Glass or glass lined (including vitrified or enameled coatings);
g.5. Tantalum or tantalum alloys;
g.6. Titanium or titanium alloys; *or*
g.7. Zirconium or zirconium alloys.
h. Multi-walled piping incorporating a leak detection port, in which all surfaces that come in direct contact with the chemical(s) being processed or contained are made from any of the following materials:
h.1. Alloys with more than 25% nickel and 20% chromium by weight;
h.2. Fluoropolymers;
h.3. Glass (including vitrified or enamelled coatings or glass lining);
h.4. Graphite or carbon-graphite;
h.5. Nickel or alloys with more than 40% nickel by weight;
h.6. Tantalum or tantalum alloys;
h.7. Titanium or titanium alloys; *or*
h.8. Zirconium or zirconium alloys.
i. Multiple-seal, canned drive, magnetic drive, bellows or diaphragm pumps, with manufacturer's specified maximum flow-rate greater than 0.6 m^3/hour, or vacuum pumps with manufacturer's specified maximum flow-rate greater than 5 m^3/hour (under standard temperature (273 K (0° C)) and pressure (101.3 kPa) conditions), and casing (pump bodies), preformed casing liners, impellers, rotors or jet pump nozzles designed for such pumps, in which all surfaces that come into direct contact with the chemical(s) being processed are made from any of the of the following materials:
i.1. Alloys with more than 25% nickel and 20% chromium by weight;
i.2. Ceramics;
i.3. Ferrosilicon;
i.4. Fluoropolymers;
i.5. Glass (including vitrified or enamelled coatings or glass lining);
i.6. Graphite or carbon-graphite;
i.7. Nickel or alloys with more than 40% nickel by weight;
i.8. Tantalum or tantalum alloys;
i.9. Titanium or titanium alloys, *or*
i.10. Zirconium or zirconium alloys.
j. Incinerators designed to destroy chemical warfare agents, chemical weapons precursors controlled by 1C350, or chemical munitions having specially designed waste supply systems, special handling facilities and an average combustion chamber temperature greater than 1000°C in which all surfaces in the waste supply system that come into direct contact with the waste products are made from or lined with any of the following materials:
j.1. Alloys with more than 25% nickel and 20% chromium by weight;
j.2. Ceramics; *or*
j.3. Nickel or alloys with more than 40% nickel by weight.

Technical Note: Carbon-graphite is a composition consisting primarily of graphite and amorphous carbon, in which the graphite is 8 percent or more by weight of the composition.

19. In Supplement No. 1 to Part 774 (the Commerce Control List), Category 2—Materials Processing, is amended by revising the List of Items Controlled section in ECCN 2B352 to read as follows:

2B352 Equipment capable of use in handling biological materials, as follows (see List of Items Controlled).

* * * * *

List of Items Controlled

Unit: Equipment in number.
Related Controls: N/A.
Related Definitions: For purposes of this entry, isolators include flexible isolators, dry boxes, anaerobic chambers and glove boxes.
Items:
a. Complete containment facilities at P3 or P4 containment level.

Technical Note: P3 or P4 (BL3, BL4, L3, L4) containment levels are as specified in the WHO Laboratory Biosafety Manual (Geneva, 1983).

b. Fermenters capable of cultivation of pathogenic microorganisms, viruses, or for toxin production, without the propagation of aerosols, having a capacity equal to or greater than 100 liters.

Technical Note: Fermenters include bioreactors, chemostats, and continuous-flow systems.

c. Centrifugal separators capable of the continuous separation of pathogenic microorganisms, without the propagation of aerosols, and having all of the following characteristics:
c.1. One or more sealing joints within the steam containment area;
c.2. A flow rate greater than 100 liters per hour;
c.3. Components of polished stainless steel or titanium; *and*
c.4. Capable of *in situ* steam sterilization in a closed state.

Technical Note: Centrifugal separators include decanters.

d. Cross (tangential) flow filtration equipment capable of continuous separation of pathogenic microorganisms, viruses, toxins, and cell cultures without the propagation of aerosols, having all of the following characteristics:
d.1. Equal to or greater than 5 square meters;
d.2. Capable of *in situ* sterilization.
e. Steam sterilizable freeze-drying equipment with a condenser capacity of 10 kgs of ice or greater in 24 hours, but less than 1,000 kgs of ice in 24 hours.
f. Protective and containment equipment, as follows:
f.1. Protective full or half suits, or hoods dependant upon a tethered external air supply and operating under positive pressure;

Technical Note: This entry does not control suits designed to be worn with self-contained breathing apparatus.

f.2. Class III biological safety cabinets or isolators with similar performance standards, *e.g.,* flexible isolators, dry boxes, anaerobic chambers, glove boxes or laminar flow hoods (closed with vertical flow).
g. Chambers designed for aerosol challenge testing with microorganisms, viruses, or toxins and having a capacity of 1 m^3 or greater.

Dated: May 23, 2002.

James J. Jochum,

Assistant Secretary for Export Administration.

[FR Doc. 02–13581 Filed 5–30–02; 8:45 am]
BILLING CODE 3510–33–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 314 and 601

[Docket No. 98N–0237]

RIN 0910–AC05

New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its new drug and biological product regulations to allow appropriate studies in animals in certain cases to provide

substantial evidence of the effectiveness of new drug and biological products used to reduce or prevent the toxicity of chemical, biological, radiological, or nuclear substances. This rule will apply when adequate and well-controlled clinical studies in humans cannot be ethically conducted and field efficacy studies are not feasible. In these situations, certain new drug and biological products that are intended to reduce or prevent serious or life-threatening conditions may be approved for marketing based on evidence of effectiveness derived from appropriate studies in animals and any additional supporting data.

DATES: This rule is effective July 1, 2002.

FOR FURTHER INFORMATION CONTACT:
Wayne H. Mitchell, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–2041;
or Karen L. Goldenthal, Center for Biologics Evaluation and Research (HFM–475), 1401 Rockville Pike, suite 370 North, Rockville, MD 20852, 301–827–3070.

SUPPLEMENTARY INFORMATION:

I. Introduction

In the **Federal Register** of October 5, 1999 (64 FR 53960), we (FDA) proposed to amend our new drug and biological product regulations to identify the information needed to provide substantial evidence of the effectiveness of certain new drug and biological products used to reduce or prevent the toxicity of chemical, biological, radiological, or nuclear substances. We are finalizing that proposed rule by adding subpart I to part 314 (21 CFR part 314) and subpart H to part 601 (21 CFR part 601).

This final rule provides for approval of certain new drug and biological products based on animal data when adequate and well-controlled efficacy studies in humans cannot be ethically conducted because the studies would involve administering a potentially lethal or permanently disabling toxic substance or organism to healthy human volunteers and field trials are not feasible prior to approval. Under this rule, in these situations, certain new drug and biological products that are intended to reduce or prevent serious or life-threatening conditions can be approved for marketing based on evidence of effectiveness derived from appropriate studies in animals, without adequate and well-controlled efficacy studies in humans (§ 314.126). In assessing the sufficiency of animal data, the agency may take into account other data, including human data, available to the agency. Under this rule, FDA can rely on the evidence from animal studies to provide substantial evidence of the effectiveness of these products when:

1. There is a reasonably well-understood pathophysiological mechanism for the toxicity of the chemical, biological, radiological, or nuclear substance and its amelioration or prevention by the product;

2. The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model (meaning the model has been adequately evaluated for its responsiveness) for predicting the response in humans;

3. The animal study endpoint is clearly related to the desired benefit in humans, which is generally the enhancement of survival or prevention of major morbidity; and

4. The data or information on the pharmacokinetics and pharmacodynamics of the product or other relevant data or information in animals and humans is sufficiently well understood to allow selection of an effective dose in humans, and it is therefore reasonable to expect the effectiveness of the product in animals to be a reliable indicator of its effectiveness in humans.

All studies subject to this rule must be conducted in accordance with preexisting requirements under the good laboratory practices (21 CFR part 58) regulations and the Animal Welfare Act (7 U.S.C. 2131 *et. seq.*).

Safety evaluation of products is not addressed in this rule. Products evaluated for effectiveness under subpart I of part 314 and subpart H of part 601 will be evaluated for safety under preexisting requirements for establishing the safety of new drug and biological products. The agency believes that the safety of most of these products can be studied in human volunteers similar to the people who would be exposed to the product. FDA recognizes that some safety data, such as data on possible adverse interactions between the toxic substance itself and the new product, may not be available. This is not expected to keep the agency from making an adequate safety evaluation. FDA's procedures and standards for evaluating the safety of new drug and biological products are sufficiently flexible to provide for the safety evaluation of products evaluated for efficacy under subpart I of part 314 and subpart H of part 601.

This rule will not apply if product approval can be based on standards described elsewhere in our regulations (for example, accelerated approval based on human surrogate markers or clinical endpoints other than survival or irreversible morbidity).[1]

II. Comments on the Proposed Rule and Our Response

We received comments on the proposed rule from two pharmaceutical companies and one physician affiliated with a university. We also received comments from the National Institutes of Health (NIH). The NIH comments were based on a prepublication draft of the proposed rule, but the comments were received too late to be addressed in the proposed rule. The NIH comments have been placed in the docket for this rule and are addressed in this document.

In addition to the changes we have made in response to comments, we have changed the titles of subpart I of part 314 and subpart H (formerly subpart G) of part 601 to better describe the scope of the subparts. Subpart I of part 314 is now entitled ''Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible'' and subpart H of part 601 is now entitled ''Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible.'' Proposed subpart G has been redesignated as subpart H in the final rule because subpart G has since been designated for regulations on postmarketing studies. Proposed §§ 601.60 through 601.65 have been renumbered §§ 601.90 through 601.95 in subpart H.

We have also changed, on our own initiative, the requirements proposed in §§ 314.610(c) and 601.61(c) (§§ 314.610(b)(3) and 601.91(b)(3) in this final rule). We have deleted the requirement that self-administered drug products approved under this rule be in unit-of-use packaging with attached patient labeling. In addition, we have eliminated the distinction between self-

[1] An example of a drug approval based on human surrogate markers is our August 30, 2000, approval of an efficacy supplement for ciprofloxacin. Ciprofloxacin HCl was approved for postexposure management of inhalational anthrax. The approval was based, in part, on human studies demonstrating that ciprofloxacin achieved serum concentrations reaching or exceeding levels associated with improved survival of animals exposed to aerosolized *Bacillus anthracis* spores. The results from these studies were combined with the knowledge of effectiveness in humans of ciprofloxacin for other bacterial infections, including pneumonia. The validity of the human surrogate marker was supported by animal studies.

administered products and products administered by health professionals.

Whether a product is self-administered or administered by a health professional, it is important to inform patient recipients that a product approved under this rule has not been studied for efficacy in humans because of ethical or feasibility reasons.[2] It is also important that patient recipients receive information about indications, dosage and administration, contraindications, reasonably foreseeable risks, adverse reactions, anticipated benefits, and drug interactions. This rule requires that all of this information be provided to patient recipients of products approved under subpart I of part 314 and subpart H of part 601.

We believe, however, that the proposed unit-of-use packaging and attached patient-labeling requirement could have had the unintended effect of hampering the distribution and dispensing of these products in the event of an emergency. The added bulk of unit-of-use packaging could have made stockpiling and transporting more difficult in many cases. The proposed requirement might also have hampered the speedy distribution of products for additional indications previously approved outside of this rule.

Applicants may meet the requirements of new §§ 314.610(b)(3) and 601.91(b)(3) in a variety of ways, as long as sponsors make provisions to get the information to patients. For example, the sponsor could provide reproducible master copies of labeling information or presentations for patient recipients that would be appropriate in the event of an emergency.

We have also changed proposed §§ 314.610(c) and 601.61(c) (§§ 314.610(b) and 601.91(b) in this final rule) to require that the patient labeling explain that, for ethical or feasibility reasons, the product's approval was based on efficacy studies conducted only in animals. This explanation will better inform patient recipients about the nature and ethical basis of the product approval under this rule and how that approval differs from approval of products based on standard human efficacy studies.

Finally, we have added to §§ 314.610(b)(1) and 601.91(b)(1) (proposed §§ 314.610(a) and 601.61(a)) a requirement that applicants include a plan or approach to fulfilling postmarketing study commitments as part of their application. We recognize that such studies normally will not be conducted unless an emergency arises that requires the product's use. Furthermore, when the product is used in an emergency, it may not be feasible for sponsors to conduct postmarketing studies in a timely manner, nor is it our intention to require sponsors to send investigators into areas of exposure. We do, however, believe that applicants can plan a postmarketing study approach, in consultation with the agency, as part of an overall response to an event.

The requirement to submit a plan for postmarketing studies is consistent with the requirements for sponsors under the accelerated approval process provided for in subpart H of part 314.

The procedures in subpart H and in this rule are similar because, to assess efficacy, both allow use of an endpoint that is not a clinical endpoint showing a benefit. Instead the rules under subpart H allow for reliance on a clinical surrogate endpoint and this rule allows for the use of animal data as an endpoint.

Postmarketing studies are critical in both of these situations to verify and describe the clinical benefit of the drug or biological product. The postmarketing studies may provide us with data that directly verify that the product provides the desired benefit in humans, such as increased survival or prevention of major morbidity.

(Comment 1) One comment suggested that we define ''lethal'' and ''permanently disabling.'' The comment expressed concern that without such definitions, subpart I of part 314 and subpart H of part 601 will be misapplied in situations where clinical testing can and should be carried out.

The definitions of ''lethal'' and ''permanently disabling'' would seem to be well understood. Although we share the concern that too expansive an interpretation of ''lethal'' or ''permanently disabling'' could lead to attempts to apply this rule when human studies are, in fact, feasible, we are also concerned that too restrictive a definition of ''lethal'' or ''permanently disabling'' could lead to failure to apply subpart I of part 314 and subpart H of part 601 in situations where they should be applied to protect the public health. We believe that, as a general matter, we must rely on the good sense and responsibility of those health professionals who will be seeking to apply subpart I of part 314 and subpart H of part 601 in the future, and on responsible review of specific cases by FDA. Nevertheless, we can provide guidance for applying subpart I of part 314 and subpart H of part 601 by clarifying that a ''lethal substance'' is one that is likely to kill at least some of the humans who have been exposed to the substance and a ''permanently disabling substance'' is one that is likely to cause a permanent physical or mental impairment that substantially limits one or more of the major life activities in at least some of the humans who have been exposed to the substance.

(Comment 2) One comment stated that the rule does not explicitly cover infectious substances and pointed out that not all infectious substances produce toxins. The comment suggested replacing ''toxic'' with ''toxic and/or infectious'' in proposed §§ 314.600 and 601.60 (§ 601.90 in this final rule).

The rule is certainly intended to cover products for treatment of infections. At some level, an infectious agent that is lethal or permanently disabling is toxic to its host, even if that agent is not itself a ''toxin'' or a producer of ''toxins'' within a strict definition of the word. Because we do not use ''toxin'' in the rule, and ''toxic'' is accurate, we do not believe we need to replace ''toxic'' with ''toxic and/or infectious'' to indicate that products for the treatment of infections may be approved under this rule.

(Comment 3) One comment noted that the proposed rule did not discuss criteria that should be applied in determining if ''an important medical need is not adequately met by currently available therapies.'' The comment suggested that we state that we will use the criteria given in our guidance for industry entitled ''Fast Track Drug Development Programs—Designation, Development, and Application Review'' (September 1998).

We have decided to eliminate the requirement that ''products would be expected to provide meaningful therapeutic benefits to patients over existing treatments,'' as well as the limitation that the toxic agent be ''without a proven treatment'' (proposed §§ 314.600 and 601.60). Recent events involving the multiple exposures to anthrax in our population, and deaths resulting from those infections, have indicated a need for a wide range of therapeutic options that, in some instances, might be inappropriately limited by requiring new products to have a therapeutic benefit over existing treatments, or to be used only in the absence of a proven treatment. Availability of a variety of drug and biological products is important because, for example, patient recipients may be allergic to one product and require another, may be intolerant of a product because of side effects, or may respond more favorably to one product

[2] In some cases, however, such as with anti-infective drug products, it would usually be expected that human data on safety and effectiveness for other indications may be available.

than another. We also believe that a wider variety of therapeutic choices will limit potential problems with availability, accessibility, and distribution of products. We have modified the final rule to address these concerns and help ensure the availability of more than one therapeutic option.

(Comment 4) One comment requested that antivenin and antitoxin products of animal origin be considered for inclusion specifically on the list of new drugs and biological products to which the rule applies.

There is no list of products that may be approved based on evidence of effectiveness from efficacy studies in animals. The rule provides criteria to determine if evidence of effectiveness from efficacy studies in animals may support approval of a product. If an antivenin or antitoxin product of animal origin meets the criteria specified in the rule, it may be approved on the basis of evidence of effectiveness from efficacy studies in animals.

(Comment 5) One comment requested that we revise proposed §§ 314.610 and 601.61 (§ 601.91 in this final rule) to state that substantiation in multiple animal species is required only where appropriate. The comment stated we should not limit ourselves to approvals only when there is substantiation in ''multiple'' animal species. The comment contended that where independent studies in a single species meet the general principles of independent substantiation as described in the guidance for industry entitled ''Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products'' (May 1998), those studies are sufficient to substantiate effectiveness as a matter of science and a requirement of substantiation in multiple species would result in an unnecessary delay of agency approval. According to the comment, these concerns are particularly important where viruses have a narrow host range and conducting efficacy trials in more than one animal species in such cases either is not feasible or provides only limited additional information that is relevant to the full-blown disease in humans. The comment suggested that the requirement of substantiation in multiple species in a given case should depend on the known host range and the availability of animal model systems.

We share some of the concerns expressed in the comment, but we believe the proposed remedy goes too far. Approval of the use of a drug lacking human evidence of effectiveness represents a significant departure from ordinary practice. There are countless examples of treatments with favorable effects in animals that did not prove effective in humans. Although this rule does, for good reason, allow reliance on animal studies when human studies cannot be conducted, in general we expect that the evidence, to be persuasive, should be developed in more than one animal species unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans. We recognize that conducting studies in more than one species can result in added expense, but we believe this is warranted because of the additional assurance they would provide.

Furthermore, reliance on our guidance entitled ''Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products'' is misplaced. That guidance was drafted to provide advice on the quantity of data from clinical studies needed to support a finding of effectiveness and, specifically, on when the agency ought to rely on a single human study. The guidance addressed cases in which the issue is the credibility of the data itself, not the relevance of the data to humans. In this rule, the issue is the ability of results from animal studies to predict the human response, and not the credibility of the animal finding itself (although, of course, the animal studies should be replicated or substantiated in each species as needed to ensure credible results). The need for multiple species in certain cases is to enhance the likelihood that the data are pertinent to humans.

We do recognize, however, that the multiple species requirement could be inappropriate or unnecessary in certain situations. For example, there may be only one species capable of reacting with a response predictive for humans. This would occur where there is only one nonhuman host for the targeted microorganism. There may also be other situations in which studies in a particular species are specifically well recognized as predictors of effectiveness in humans. Thus, circumstances in which the agency will rely on evidence from studies in one animal species to provide substantial evidence of the effectiveness of these products in humans would generally be limited to situations where the study model is sufficiently well-recognized so as to render studies in multiple species unnecessary. In addition, other human data for the product could provide support for such approvals.

Accordingly, we have changed proposed §§ 314.610 and 601.61 (§ 601.91(c) in this final rule) to require that approval be based on studies in more than one animal species unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans. The agency believes that demonstrating effectiveness in studies conducted in a single animal species using a well-characterized animal model will most often be done for anti-infective drug products. The pathophysiological mechanisms of infectious diseases are usually very well understood, and animal models for many infectious diseases have been studied for years and are very well characterized.

(Comment 6) One comment suggested we remove the requirement that there be a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product. The comment stated it is hard to say when we understand something reasonably well and that, if we decide to retain the requirement, we should state at what level (e.g., cellular, molecular) the mechanism must be understood.

A disease's or toxin's mechanism of action does not need to be understood before a safe and effective treatment or preventative can be devised. Quinine and Jenner's smallpox vaccine were both developed before the acceptance of the germ theory of disease. Neither is there a general requirement that an applicant who is relying on human testing to establish effectiveness demonstrate the mechanism of action of the drug or biological product that is the subject of the marketing application. It is generally sufficient to demonstrate that a product is safe and effective. It is generally not required that an applicant demonstrate how or why the product is safe and effective.

It is true that a pathophysiologic understanding of a disease and treatment is not required when human studies are used to support approval. In the case of human drug or biological products approved on the basis of evidence of effectiveness from studies in animals, however, we are requiring an understanding of the mechanism of the toxic substance or infectious organism and its prevention or reduction by the product. This understanding helps provide assurance that the efficacy data from studies in animals can be applied to humans. We have not specified exactly what degree of pathophysiologic understanding is needed, and that will be a matter of judgment. The level of understanding could range from a complete understanding of how a toxic

substance works at the cellular level in both human and animal cells together with a clear understanding of what the antidote does at the molecular level to a less complete understanding. The level of required understanding of the mechanism of action of the toxic substance or infectious organism and the product may vary from toxic substance to toxic substance or infectious organism to infectious organism and could even vary from one product to another intended to treat the same condition.

(Comment 7) One comment suggested that an institutional review board (IRB) or other ethical scientific review body determine if it would be unethical to conduct studies in humans. The comment also said we do not mention who would make the determination that it would be unethical to conduct studies in humans.

The final determination that it is unethical to conduct studies in humans will be made by the reviewing officials in FDA. We anticipate that in most cases the determination as to whether it would be unethical to conduct studies in humans will not be difficult. In those cases that are difficult, the views of one or more IRBs, individual ethicists and clinicians, and FDA advisory committees could be sought by a sponsor or FDA. A case where such a consultation could be useful is one in which a putatively subtoxic dose would be used in humans to establish at least a mechanism for protection, if not actual protection.

(Comment 8) One comment noted that we said in the proposed rule:

> The agency also intends in most cases to consult on applications to market such products with an advisory committee, supplemented with appropriate expert consultants, in meetings open to the public in order to receive expert advice on whether a particular set of animal data support efficacy of a product under this rule (64 FR 53960 at 53964 and 53965).

The comment asked us to consider requiring consultation with an advisory committee either before conducting the animal studies or before approval of the product, or both.

We want to reiterate our statement in the proposed rule that we intend usually to consult with an advisory committee during the approval process. Indeed, we may consult with an advisory committee more than once on a single product if circumstances warrant it. Consultation with an advisory committee could occur early in the development process, to discuss whether the concept of using certain animal data to support efficacy is reasonable.

Even though consultation with an advisory committee is generally desirable, it is not always practical. For example, products reviewed under this rule may be part of the response to a public health emergency; therefore, there may not be time to convene an advisory committee. Accordingly, we believe that it would be inappropriate to absolutely require consultation with an advisory committee.

(Comment 9) One comment questioned whether patient labeling is adequate to inform patients that a product has been approved on the basis of animal efficacy data, particularly in situations where military personnel are ordered to take a product approved under this rule. The comment did not suggest an alternative to the provisions of the rule.

Sections 314.610(b)(3) and 609.91(b)(3) provide that for products or specific indications approved under this rule, applicants must prepare, as part of their proposed labeling, labeling to be provided to patients or potential patients. The patient labeling, written in language that can be easily understood by the general public, must explain that, for ethical or feasibility reasons, the product's approval was based on efficacy studies conducted in animals alone. The labeling must give the product's indication(s), directions for use (dosage and administration), contraindications, a description of any reasonably foreseeable risks, adverse reactions, anticipated benefits, drug interactions, and any other relevant information required by FDA at the time of approval. If possible, the patient labeling must be available with the product to be provided to patients or potential patients prior to administration or dispensing of the product for the use approved under this rule. We intend that in interpreting §§ 314.610(b)(3) and 601.91(b)(3), the word ''possible'' be given its ordinary and literal meaning. Situations in which it would be inconvenient or require some effort to make the labeling available for patients should not be equated with situations in which it would be impossible to do so.

These provisions, coupled with communications within a health care provider-patient relationship should, as a general matter in both civilian and military contexts, adequately ensure that patients are informed that the product they are taking has been approved based on animal efficacy data.

(Comment 10) One comment suggested that labeling a drug or biological product approved on the basis of evidence of effectiveness from studies in animals as ''FDA approved'' is misleading, because patients would assume that the product had been approved based on human studies. The comment suggested that we treat the product as an investigational new drug, but waive certain requirements generally applied to investigational new drugs, if those requirements would provide obstacles to the product's use in an emergency.

We agree that the labeling would be misleading if information were not included to explain to patients or potential patients that the effectiveness of the product was demonstrated in animals not humans, and that this reliance on animal efficacy data was based on ethical and feasibility concerns. Therefore, under sections 502(a) and 701(a) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352(a) and 372(a)) (and consistent with the legal authority cited in the preamble to the proposed rule (64 FR 53960 at 53964)), we have revised the language in §§ 314.610(b)(3) and 601.91(b)(3) to require that this information be included in the patient labeling.

Where the evidence of effectiveness comes from studies in animals, regulating new drug or biological products as investigational drugs presents several difficulties. These difficulties have led us to this rulemaking. The proposed rule describes our concerns with relying solely on the investigational new drug regulations (64 FR 53960 at 53963) for such approvals. There may be cases, however, when an application does not meet the criteria of this rule, and approval of the product is not feasible. Should an emergency situation arise under such circumstances, it is conceivable that the product could be used under the investigational new drug regulations.

(Comment 11) Another comment suggested that, unless ''lay persons'' may use the product, we prohibit advertising of drug or biological products approved on the basis of evidence of effectiveness from studies in animals. The comment further recommended stringent controls on the advertising of products that could be used by ''lay persons.''

Such a sweeping prohibition would likely give rise to constitutional issues regarding the regulation of commercial speech. In addition, the suggestion presents serious public health concerns. A prohibition on advertising could limit health care providers' and public health and emergency preparedness officials' awareness of the products approved under this rule. Limiting awareness of these products, which are intended to

reduce or prevent life-threatening or disabling toxicity, does not seem desirable or appropriate.

We believe that the advertising provisions in §§ 314.640 and 601.94 of this rule provide adequate protection against false or misleading advertising, and no additional requirements are needed. As discussed in the preamble to the proposed rule (64 FR 53960 at 53964), we proposed the requirements pertaining to promotional materials in order to provide for the safe and effective use of these products. These requirements, along with others, are similar to those in the accelerated approval regulations in subpart H of part 314 and in subpart E of part 601. In issuing the accelerated approval regulations, we stated that the special circumstances under which those products would be approved and the possibility that promotional materials could adversely affect the sensitive risk/benefit balance justified review of promotional materials before and after approval (57 FR 58942 at 58949). Similarly, the special circumstances of all product approvals under subpart I of part 314 and subpart H of part 601 and the possibility that promotional materials could adversely affect the even more sensitive risk/benefit balance justifies advance review of promotional materials.

We intend to review all such promotional materials under these new regulations promptly, and to notify the applicant of any identified problems as soon as possible (see also 57 FR 58942 at 58950). Also as with the accelerated approval regulations' requirements for promotional materials (§§ 314.560 and 601.46), FDA may terminate the requirements for advance submission of promotional materials under these new regulations at §§ 314.650 and 601.95 if the agency determines, on its own initiative or in response to a petition submitted by the sponsor, that the requirements are no longer necessary for safe and effective use of the product. When we remove the requirement for advance submission of promotional materials, we will continue to offer a prompt review of all voluntarily submitted promotional materials.

(Comment 12) We received some comments addressing questions posed in section VII, ''Discussion,'' of the proposed rule. In this final rule, we have addressed comments that dealt with the rule itself. Comments that dealt with questions related to the application of this rule, rather than the requirements, will be addressed if and when we draft a guidance on this subject.

III. Legal Authority

We did not receive any comments discussing our legal authority to approve new drugs and biological products based on evidence of effectiveness from studies in animals. We have concluded, for the reasons set out in section V of the proposed rule, ''Legal Authority,'' (64 FR 53960 at 53964), that we have the legal authority to approve new drugs and biological products based on evidence of effectiveness from studies in animals.

(Comment 13) We received a comment asserting that under the court's holding in *American Pharmaceutical Association* v. *Weinberger*, 377 F.Supp. 824 (D.C.D.C. 1974) *aff'd sub nom. American Pharmaceutical Association* v. *Mathews*, 530 F.2d 1054 (D.C. Cir. 1976) (*per curiam*), we do not have the legal authority to impose the distribution controls proposed in §§ 314.610(b) and 601.61(b) (§§ 314.610(b)(2) and 601.91(b)(2) in this final rule). The comment asked that, if we disagree with their characterization of the law, distribution controls not be applied just because a product was approved under the provisions of this rule. The comment also asked that we give examples of situations where we would impose distribution restrictions.

For a full discussion of FDA's authority to impose distribution restrictions to ensure the safe use of drug products, see the agency's proposed and final rules amending part 314 by adding subpart H on accelerated approval of new drugs for serious or life-threatening illnesses (proposed rule at 57 FR 13234, April 15, 1992; final rule at 57 FR 59842, December 11, 1992). Those rules relied on sections 501, 502, 503, 505, and 701 of the act (21 U.S.C. 351, 352, 353, 355, and 372) as authority for FDA to issue regulations to help ensure the safety and effectiveness of new drugs.

We agree with the comment that distribution controls should not be placed on a product solely because it is approved under the provisions of this rule. New §§ 314.610(b)(2) and 601.91(b)(2) authorize distribution controls—they do not require them.

We do not believe it would be useful to give examples of situations where distribution controls may be necessary to ensure safe use of the product. Products approved under this rule could be indicated for widely differing conditions, and those products could be used in unique circumstances presenting many distinct safety concerns. It would not be practical to try to devise a list of representative examples of situations where distribution controls would be appropriate.

IV. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

VI. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612) (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Public Law 104–121)) and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Unless the agency certifies that the rule is not expected to have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant economic impact of a rule on small entities. Section 202 of the Unfunded Mandates Reform Act (Public Law 104–4) requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million in any one year (adjusted annually for inflation).

The agency has determined that the rule is consistent with the principles set forth in the Executive order and in these statutes. FDA finds that this rule will not have an effect on the economy that exceeds $100 million in any one year (adjusted for inflation). The current inflation-adjusted statutory threshold is about $110 million. Therefore, no further analysis is required under the Unfunded Mandates Reform Act. Because this rule does not impose any new costs on small entities, FDA certifies that this rule will not result in a significant economic impact on a substantial number of small entities. Thus, the agency need not prepare a Regulatory Flexibility Analysis. The agency reached the same conclusions in its proposed rule. FDA has not received any new information or comments that would alter its previous determinations.

VII. The Paperwork Reduction Act of 1995

This final rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection provisions are shown below with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: New Drug and Biological Products; Animal Efficacy Studies.

Description: FDA is amending its new drug and biological product regulations to allow appropriate studies in animals in certain cases to provide substantial evidence of effectiveness of new drug and biological products used to reduce or prevent the toxicity of chemical, biological, radiological, or nuclear substances when adequate and well-controlled efficacy studies in humans cannot be ethically conducted because the studies would involve administering a potentially lethal or permanently disabling toxic substance or organism to healthy human volunteers and field trials are not feasible prior to approval. In these circumstances, when it may be impossible to demonstrate effectiveness through adequate and well-controlled studies in humans, FDA is providing that certain new drug and biological products intended to treat or prevent serious or life-threatening conditions could be approved for marketing based on studies in animals, without the traditional efficacy studies in humans. FDA is taking this action because it recognizes the importance of improving medical response capabilities to the use of lethal or permanently disabling chemical, biological, radiological, and nuclear substances in order to protect individuals exposed to these substances.

Respondent Description: Businesses and other for-profit organizations, and nonprofit institutions.

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
314.610(b)(2) and 314.630 601.91(b)(2) and 601.93	1	1	1	5	5
314.610(b) and 314.640 601.91(b) and 601.94	1	1	1	240	240
Total					245

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

TABLE 2.—ESTIMATED ANNUAL DISCLOSURE/RECORDKEEPING BURDEN[1]

21 CFR Section	No. of Record-keepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
314.610(b)(2) and 314.630 601.91(b)(2) and 601.93	1	1	1	1	1
314.610(b) 601.91(b)	1	1	1	1	1
Total					2

[1]There are no capital costs or operating and maintenance costs with this collection of information.

FDA estimates that only one application of this nature may be submitted every 3 years; however, for calculation purposes, FDA is estimating the submission of one application annually. FDA estimates 240 hours for a manufacturer of a new drug or biological product to develop patient labeling and to submit the appropriate information and promotional labeling to FDA. At this time, FDA cannot estimate the number of postmarketing reports for adverse drug or biological experiences associated with a newly approved drug or biological product. Therefore, FDA is using one report for purposes of this information collection. These reports are required under parts 310 and 600 (21 CFR parts 310 and 600), and 314. Any burdens associated with these requirements will be reported under the adverse experience reporting (AER) information collection requirements. The estimated hours for postmarketing reports range from 1 to 5 hours based on previous estimates for AER; however FDA is estimating 5 hours for the purpose of this information collection.

The majority of the burden for developing the patient labeling is included under the reporting requirements; therefore, minimal burden is calculated for providing the guide to patients. As discussed previously, no burden can be calculated at this time for the number of AER reports that may be submitted after approval of a new drug or biologic. Therefore, the number of records that may be maintained also cannot be determined. Any burdens associated with these requirements will be reported under the AER information collection requirements. The estimated recordkeeping burden of 1 hour is based on previous estimates for the recordkeeping requirements associated with the AER system.

The information collection provisions in this final rule have been approved under OMB control number 0910–0423. This approval expires December 31, 2002. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

List of Subjects

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 314 and 601 are amended as follows:

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

1. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 356, 356a, 356b, 356c, 371, 374, 379e.

2. Subpart I, consisting of §§ 314.600 through 314.650, is added to read as follows:

Subpart I—Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible

Sec.

Subpart I—Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible

§ 314.600 Scope.

This subpart applies to certain new drug products that have been studied for their safety and efficacy in ameliorating or preventing serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances. This subpart applies only to those new drug products for which: Definitive human efficacy studies cannot be conducted because it would be unethical to deliberately expose healthy human volunteers to a lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substance; and field trials to study the product's effectiveness after an accidental or hostile exposure have not been feasible. This subpart does not apply to products that can be approved based on efficacy standards described elsewhere in FDA's regulations (e.g., accelerated approval based on surrogate markers or clinical endpoints other than survival or irreversible morbidity), nor does it address the safety evaluation for the products to which it does apply.

§ 314.610 Approval based on evidence of effectiveness from studies in animals.

(a) FDA may grant marketing approval for a new drug product for which safety has been established and for which the requirements of § 314.600 are met based on adequate and well-controlled animal studies when the results of those animal studies establish that the drug product is reasonably likely to produce clinical benefit in humans. In assessing the sufficiency of animal data, the agency may take into account other data, including human data, available to the agency. FDA will rely on the evidence from studies in animals to provide substantial evidence of the effectiveness of these products only when:

(1) There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product;

(2) The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans;

(3) The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity; and

(4) The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.

(b) Approval under this subpart will be subject to three requirements:

(1) *Postmarketing studies.* The applicant must conduct postmarketing studies, such as field studies, to verify and describe the drug's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical. Such postmarketing studies would not be feasible until an exigency arises. When such studies are feasible, the applicant must conduct such studies with due diligence. Applicants must include as part of their application a plan or approach to postmarketing study commitments in the event such studies become ethical and feasible.

(2) *Approval with restrictions to ensure safe use.* If FDA concludes that a drug product shown to be effective under this subpart can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to ensure safe use of the drug product, commensurate with the specific safety concerns presented by the drug product, such as:

(i) Distribution restricted to certain facilities or health care practitioners with special training or experience;

(ii) Distribution conditioned on the performance of specified medical procedures, including medical followup; and

(iii) Distribution conditioned on specified recordkeeping requirements.

(3) *Information to be provided to patient recipients.* For drug products or specific indications approved under this subpart, applicants must prepare, as part of their proposed labeling, labeling to be provided to patient recipients. The patient labeling must explain that, for ethical or feasibility reasons, the drug's approval was based on efficacy studies conducted in animals alone and must give the drug's indication(s), directions for use (dosage and administration), contraindications, a description of any reasonably foreseeable risks, adverse reactions, anticipated benefits, drug interactions, and any other relevant information required by FDA at the time of approval. The patient labeling must be available with the product to be provided to patients prior to administration or dispensing of the drug product for the use approved under this subpart, if possible.

§ 314.620 Withdrawal procedures.

(a) *Reasons to withdraw approval.* For new drugs approved under this subpart, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

(1) A postmarketing clinical study fails to verify clinical benefit;

(2) The applicant fails to perform the postmarketing study with due diligence;

(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the drug product;

(4) The applicant fails to adhere to the postmarketing restrictions applied at the time of approval under this subpart;

(5) The promotional materials are false or misleading; or

(6) Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

(b) *Notice of opportunity for a hearing.* The Director of the Center for Drug Evaluation and Research (CDER) will give the applicant notice of an opportunity for a hearing on CDER's proposal to withdraw the approval of an application approved under this subpart. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) *Submission of data and information.* (1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.

(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the **Federal Register** in accordance with §§ 12.32(e) and 15.20 of this chapter.

(3) An applicant who requests a hearing under this section must, within 30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) *Separation of functions.* Separation of functions (as specified in § 10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

(e) *Procedures for hearings.* Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:

(1) An advisory committee duly constituted under part 14 of this chapter will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.

(2) The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of CDER may question any person during or at the conclusion of the person's presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) *Judicial review.* The Commissioner of Food and Drugs' decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a petition for a stay of action under § 10.35 of this chapter.

§ 314.630 Postmarketing safety reporting.

Drug products approved under this subpart are subject to the postmarketing recordkeeping and safety reporting requirements applicable to all approved drug products, as provided in §§ 314.80 and 314.81.

§ 314.640 Promotional materials.

For drug products being considered for approval under this subpart, unless otherwise informed by the agency, applicants must submit to the agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

§ 314.650 Termination of requirements.

If FDA determines after approval under this subpart that the requirements established in §§ 314.610(b)(2), 314.620, and 314.630 are no longer necessary for the safe and effective use of a drug product, FDA will so notify the applicant. Ordinarily, for drug products approved under § 314.610, these requirements will no longer apply when FDA determines that the postmarketing study verifies and describes the drug product's clinical benefit. For drug products approved under § 314.610, the restrictions would no longer apply when FDA determines that safe use of the drug product can be ensured through appropriate labeling. FDA also retains the discretion to remove specific postapproval requirements upon review of a petition submitted by the sponsor in accordance with § 10.30 of this chapter.

PART 601—LICENSING

3. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: 15 U.S.C. 1451–1561; 21 U.S.C. 321, 351, 352, 353, 355, 356b, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263, 264; sec. 122, Pub. L. 105–115, 111 Stat. 2322 (21 U.S.C. 355 note).

4. Subpart H, consisting of §§ 601.90 through 601.95, is added to read as follows:

Subpart H—Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible

Sec.

Subpart H—Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible

§ 601.90 Scope.

This subpart applies to certain biological products that have been studied for their safety and efficacy in ameliorating or preventing serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances. This subpart applies only to those biological products for which: Definitive human efficacy studies cannot be conducted because it would be unethical to deliberately expose healthy human volunteers to a lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substance; and field trials to study the product's efficacy after an accidental or hostile exposure have not been feasible. This subpart does not apply to products that can be approved based on efficacy standards described elsewhere in FDA's regulations (e.g., accelerated approval based on surrogate markers or clinical endpoints other than survival or irreversible morbidity), nor does it address the safety evaluation for the products to which it does apply.

§ 601.91 Approval based on evidence of effectiveness from studies in animals.

(a) FDA may grant marketing approval for a biological product for which safety has been established and for which the requirements of § 601.90 are met based on adequate and well-controlled animal studies when the results of those animal studies establish that the biological product is reasonably likely to produce clinical benefit in humans. In assessing the sufficiency of animal data, the agency may take into account other data, including human data, available to the agency. FDA will rely on the evidence from studies in animals to provide substantial evidence of the effectiveness of these products only when:

(1) There is a reasonably well-understood pathophysiological mechanism of the toxicity of the

substance and its prevention or substantial reduction by the product;

(2) The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans;

(3) The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity; and

(4) The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.

(b) Approval under this subpart will be subject to three requirements:

(1) *Postmarketing studies.* The applicant must conduct postmarketing studies, such as field studies, to verify and describe the biological product's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical. Such postmarketing studies would not be feasible until an exigency arises. When such studies are feasible, the applicant must conduct such studies with due diligence. Applicants must include as part of their application a plan or approach to postmarketing study commitments in the event such studies become ethical and feasible.

(2) *Approval with restrictions to ensure safe use.* If FDA concludes that a biological product shown to be effective under this subpart can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to ensure safe use of the biological product, commensurate with the specific safety concerns presented by the biological product, such as:

(i) Distribution restricted to certain facilities or health care practitioners with special training or experience;

(ii) Distribution conditioned on the performance of specified medical procedures, including medical followup; and

(iii) Distribution conditioned on specified recordkeeping requirements.

(3) *Information to be provided to patient recipients.* For biological products or specific indications approved under this subpart, applicants must prepare, as part of their proposed labeling, labeling to be provided to patient recipients. The patient labeling must explain that, for ethical or feasibility reasons, the biological product's approval was based on efficacy studies conducted in animals alone and must give the biological product's indication(s), directions for use (dosage and administration), contraindications, a description of any reasonably foreseeable risks, adverse reactions, anticipated benefits, drug interactions, and any other relevant information required by FDA at the time of approval. The patient labeling must be available with the product to be provided to patients prior to administration or dispensing of the biological product for the use approved under this subpart, if possible.

§ 601.92 Withdrawal procedures.

(a) *Reasons to withdraw approval.* For biological products approved under this subpart, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

(1) A postmarketing clinical study fails to verify clinical benefit;

(2) The applicant fails to perform the postmarketing study with due diligence;

(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the biological product;

(4) The applicant fails to adhere to the postmarketing restrictions applied at the time of approval under this subpart;

(5) The promotional materials are false or misleading; or

(6) Other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use.

(b) *Notice of opportunity for a hearing.* The Director of the Center for Biologics Evaluation and Research (CBER) will give the applicant notice of an opportunity for a hearing on CBER's proposal to withdraw the approval of an application approved under this subpart. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) *Submission of data and information.* (1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.

(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the **Federal Register** in accordance with §§ 12.32(e) and 15.20 of this chapter.

(3) An applicant who requests a hearing under this section must, within 30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) *Separation of functions.* Separation of functions (as specified in § 10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

(e) *Procedures for hearings.* Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:

(1) An advisory committee duly constituted under part 14 of this chapter will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.

(2) The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of CBER may question any person during or at the conclusion of the person's presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) *Judicial review.* The Commissioner of Food and Drugs' decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a petition for a stay of action under § 10.35 of this chapter.

§ 601.93 Postmarketing safety reporting.

Biological products approved under this subpart are subject to the postmarketing recordkeeping and safety reporting applicable to all approved biological products.

§ 601.94 Promotional materials.

For biological products being considered for approval under this subpart, unless otherwise informed by the agency, applicants must submit to the agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

601.95 Termination of requirements.

If FDA determines after approval under this subpart that the requirements established in §§ 601.91(b)(2), 601.92, and 601.93 are no longer necessary for the safe and effective use of a biological product, FDA will so notify the applicant. Ordinarily, for biological products approved under § 601.91, these requirements will no longer apply when FDA determines that the postmarketing study verifies and describes the biological product's clinical benefit. For biological products approved under § 601.91, the restrictions would no longer apply when FDA determines that safe use of the biological product can be ensured through appropriate labeling. FDA also retains the discretion to remove specific postapproval requirements upon review of a petition submitted by the sponsor in accordance with § 10.30 of this chapter.

Dated: May 23, 2002.

Lester M. Crawford,

Deputy Commissioner.

[FR Doc. 02–13583 Filed 5–30–02; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 1

[TD 8998]

RIN 1545–BA74

Loss Limitation Rules

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Temporary regulations.

SUMMARY: This document contains amendments to temporary regulations issued under sections 337(d) and 1502. The amendments clarify certain aspects of the temporary regulations relating to the deductibility of losses recognized on dispositions of subsidiary stock by members of a consolidated group. The amendments in these temporary regulations apply to corporations filing consolidated returns, both during and after the period of affiliation, and also affect purchasers of the stock of members of a consolidated group. The text of these temporary regulations also serves as the text of the proposed regulations set forth in the notice of proposed rulemaking on this subject in the Proposed Rules section in this issue of the **Federal Register**.

DATES: *Effective Date:* These regulations are effective May 31, 2002.

Applicability Date: For dates of applicability *see* § 1.337(d)–2T(g) and 1.1502–20T(i).

FOR FURTHER INFORMATION CONTACT: Sean P. Duffley (202) 622–7530 or Lola L. Johnson (202) 622–7550 (not toll-free numbers).

SUPPLEMENTARY INFORMATION:

Paperwork Reduction Act

The collection of information contained in these regulations has been previously reviewed and approved by the Office of Management and Budget under control number 1545–1774. Responses to this collection of information are voluntary. No material changes to this collection of information are made by these regulations.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a valid control number assigned by the Office of Management and Budget.

Books or records relating to the collection of information must be retained as long as their contents may become material in the administration of any internal revenue law. Generally, tax returns and tax return information are confidential, as required by 26 U.S.C. 6103.

Background

On March 12, 2002, the IRS and Treasury published in the **Federal Register** at 67 FR 11034 (2002–13 I.R.B. 668) temporary regulations under sections 337(d) and 1502 (the temporary regulations). The temporary regulations set forth rules that limit the deductibility of loss recognized by a consolidated group on the disposition of stock of a subsidiary member and that require certain basis reductions on the deconsolidation of stock of a subsidiary member. Section 1.1502–20T(i) of the temporary regulations provides that, in the case of a disposition or deconsolidation of a subsidiary before March 7, 2002, and for such transactions effected pursuant to a binding written contract entered into before March 7, 2002, that was in continuous effect until the disposition or deconsolidation, a consolidated group may determine the amount of allowable stock loss or basis reduction by applying § 1.1502–20 in its entirety, § 1.1502–20 without regard to the duplicated loss component of the loss disallowance rule, or § 1.337(d)-2T. For dispositions and deconsolidations that occur on or after March 7, 2002, and that are not within the scope of the binding contract rule, § 1.1502–20T(i) provides that allowable loss and basis reduction are determined under § 1.337(d)-2T, not § 1.1502–20.

Explanation of Provisions

Since the publication of the temporary regulations, several questions have been raised concerning the interpretation and application of the temporary regulations. In response to these questions, the IRS and Treasury are promulgating the regulations in this Treasury decision as temporary regulations to clarify and amend the temporary regulations as described below in this preamble. The following paragraphs describe these amendments.

Netting Rule

Commentators requested that § 1.337(d)-2T be amended to provide a netting rule similar to that set forth in § 1.1502–20(a)(4), pursuant to which gain and loss from certain dispositions of stock may be netted. This Treasury decision adds § 1.337(d)-2T(a)(4) to provide such a rule and also adds § 1.337(d)-2T(b)(4), which provides a similar netting rule for basis reductions on deconsolidations of subsidiary stock.

Time For Filing Election Described in § 1.1502–20T(i)

Section 1.1502–20T(i) currently provides that an election to determine allowable loss by applying § 1.1502–20 (without regard to the duplicated loss component of the loss disallowance rule) or § 1.337(d)–2T must be made by including a statement with or as part of the original return for the taxable year that includes the later of March 7, 2002, and the date of the disposition or deconsolidation of the stock of the subsidiary, or with or as part of an amended return filed before the date the original return for the taxable year that includes March 7, 2002, is due. Commentators noted that this provision may not permit the election to be made on an original return for the 2001 taxable year where the disposition occurs during the 2001 taxable year. The IRS and Treasury believe that it is appropriate to permit the election to be made on such a return. Therefore, this Treasury decision amends § 1.1502–20T(i) to provide that the statement may be filed with or as part of a timely filed (including any extensions) original return for any taxable year that includes any date on or before March 7, 2002. In addition, if the date of the disposition or deconsolidation of the stock of the subsidiary is after March 7, 2002, the statement may be filed with or as part of a timely filed (including any extensions) original return for the taxable year that includes such date. This latter alternative effectively permits the statement to be filed with the original return that includes the date

Appendix E

Department of Defense Memorandum:
Reintroduction of the Anthrax Vaccine Immunization Program

DEPUTY SECRETARY OF DEFENSE
1010 DEFENSE PENTAGON
WASHINGTON, DC 20301-1010

JUN 28 2002

MEMORANDUM FOR SECRETARIES OF THE MILITARY DEPARTMENTS
CHAIRMAN OF THE JOINT CHIEFS OF STAFF
UNDER SECRETARIES OF DEFENSE
ASSISTANT SECRETARIES OF DEFENSE
GENERAL COUNSEL, DEPARTMENT OF DEFENSE
INSPECTOR GENERAL, DEPARTMENT OF DEFENSE
DIRECTORS OF DEFENSE AGENCIES
COMMANDANT OF THE US COAST GUARD

SUBJECT: Reintroduction of the Anthrax Vaccine Immunization Program (AVIP)

Food and Drug Administration (FDA) approval of the manufacturer's renovated facility restores the availability of anthrax vaccine. FDA has determined that the current anthrax vaccine is safe and effective in protecting against all forms of anthrax infection, a scientific conclusion recently supported by the Institute of Medicine.

Current intelligence assessments indicate that the anthrax threat to Department of Defense (DoD) forces is real. The Department's goal is to protect all forces against anthrax as a part of the Department's Force Health Protection program. Steps are being taken by the Department to ensure protection of U.S. servicemembers and DoD personnel against the threat of anthrax and other potential bioweapon agents, including improved intelligence, detection, and surveillance capabilities, protective clothing and equipment, and new generation vaccines and other medical countermeasures.

At this time, the DoD will resume an Anthrax Vaccine Immunization Program (AVIP) consistent with FDA guidelines and the best practice of medicine, beginning with military personnel, and Emergency-Essential DoD civilians and contractors, at higher risk whose performance is essential for certain mission critical capabilities. Vaccination is mandatory for these personnel, except as provided under applicable medical and administrative exemption policies.

The scope of the AVIP shall encompass personnel assigned to or deployed for more than 15 days in higher threat areas whose performance is essential for certain mission critical capabilities. Near-term AVIP implementation may also include other personnel determined by the Assistant Secretary of Defense for Health Affairs, in consultation with the Chairman of the Joint Chiefs of Staff, to be at higher

risk of exposure to anthrax as conditions change. Vaccinations shall begin, to the extent feasible, 45 days prior to deployment or arrival in higher threat areas.

For personnel who are covered under this new policy, who had previously begun the six shot series but had not completed it, resumption of their vaccination series will begin immediately. For personnel whose six shot series was interrupted, but who are not covered under the new policy, completion of their vaccination series will be deferred until further notice; resumption will begin when feasible, subject to availability of vaccine. Personnel currently being immunized—designated special mission units, manufacturing and DoD research personnel, and Congressionally mandated anthrax vaccine researchers—will continue with their scheduled vaccinations and annual booster shots.

The Under Secretary of Defense for Personnel and Readiness shall issue policy guidance on the medical and administrative aspects of the AVIP. Effective program implementation continues to be the responsibility of the Secretary of the Army as the Executive Agent for the AVIP and the designated senior military officers of the Services.

Appendix F

Institute of Medicine: *CDC Anthrax Vaccine Safety & Efficacy Research Program. Interim Report* Findings and Recommendations[1]

FINDINGS

- The CDC either has not developed, or has not communicated, a comprehensive plan for the CDC's role in anthrax vaccine safety and efficacy research.
- Despite the absence of a comprehensive plan, the CDC's research program includes appropriate and well-conceived scientific projects that are generally responsive to the Congressional mandate.
- The CDC's research program also includes many particular projects that presently are quite underdeveloped or include unspecified elements.
- Areas of potential collaboration between the CDC, DoD and NIH exist and should be more fully exploited, notably, for example the use of DoD databases such as the Defense Medical Surveillance System (DMSS).
- The areas of potential deficit or concern can be remedied.

GENERAL RECOMMENDATIONS

- The CDC should produce a comprehensive description of its research program, including statements of the goals of the program and how the plans now undertaken will meet those goals. In addition, the CDC should continue and complete development of the individual projects in the research program.
- The CDC should consider engaging protocol design consultants representing broad scientific expertise who would provide immediate and direct consultation on specific technical matters of study design and execution.
- The CDC should continue and strengthen collaboration with DoD and NIH wherever possible, including for example much more extensive use of DoD databases such as the Defense Medical Surveillance System (DMSS).

[1] These findings and recommendations appear in *CDC Anthrax Vaccine Safety and Efficacy Research Program. Interim Report* (Institute of Medicine, 2001; Washington, D.C.: National Academy Press). The complete report is available on the Internet at http://www.nap.edu/catalog/10157.html.

PROJECT-SPECIFIC RECOMMENDATIONS

- The committee recommends that, in the human clinical trial, the CDC should consider including a study group immunized at the start of the series (time zero), and one and six months later, followed by placebo, in order to assess adequacy of a simplified three-dose regimen in the development of immediate and long-term immunity to anthrax.
- The committee recommends careful selection of statistical methodologies, as certain techniques including intent-to-treat analysis may be less appropriate in developing conclusions for what will eventually be a military application than they would be for general civilian vaccine development.
- The committee recommends that the CDC consider, in addition to the proposed clinical trial, prospectively designed pharmacoepidemiologic study of military vaccine recipients with both active surveillance and historical data from DMSS for moderate and severe adverse events in order to assess sex or gender and perhaps other risk factors for adverse events among military personnel receiving the anthrax vaccine.
- The committee recommends that the CDC consider both the addition of a passive antibody transfer study, and that the animal trial dose ranging study design include a more gradual dilution series.
- The committee recommends that the use of microarrays receive further critical attention and precise evaluation of what information will be gleaned and how it will be interpreted and applied to anthrax vaccine recipients.
- The committee recommends that the CDC consider expanding the design phase of the KAB study of military personnel regarding the anthrax vaccine to include cognitive and psychometric tests and a pilot survey in order to design both the educational interventions and the survey that will relate to them, in order to refine the sampling plan.
- The committee recommends that the CDC consider expanding the design phase of the KAB study of military vaccine providers regarding VAERS reporting to include cognitive and psychometric tests and a pilot survey, in order to design both the educational interventions and the survey that will relate to them and possibly reduce the number of subjects.
- The committee recommends that the CDC consider including a study of the KAB of health care providers regarding the anthrax vaccine in the study now designed to assess only KAB on VAERS reporting.
- The committee recommends that the CDC make use of independent sources of information concerning vaccine adverse reactions in the military, such as the DMSS, when assessing any monitoring of, or modification to, VAERS reporting practices and VAERS analysis.
- The committee recommends that the CDC consider including additional items with the SF-36 specific to adverse events possibly associated with immunization, and clearly indicate how the use of the SF-36 will be included in the protocol.

Appendix G

Institute of Medicine: *The Anthrax Vaccine: Is It Safe? Does It Work?* Findings and Recommendations[1]

CHAPTER 3

Findings

- The randomized field study carried out by Brachman and colleagues (1962) provides solid evidence indicating the efficacy of a vaccine similar to AVA against *B. anthracis* infection. The subsequent CDC data are supportive. However, the small number of inhalational cases in those studies provides insufficient information to allow a conclusion about the vaccine's efficacy against inhalational infection to be made.
- Because additional clinical trials to test the efficacy of AVA in humans are not feasible and challenge trials with volunteers are unethical, by necessity, animal models represent the only sources of the supplementary data needed to evaluate AVA's efficacy.
- The macaque and the rabbit are adequate animal models for evaluation of the efficacy of AVA for the prevention of inhalational anthrax.
- It is unlikely that either naturally occurring or anthrax strains with bioengineered protective antigen could both evade AVA and cause the toxicity associated with anthrax.
- The available data indicate that immunity to anthrax is associated with the presence of antibody to protective antigen.
- The committee finds that the available evidence from studies with humans and animals, coupled with reasonable assumptions of analogy, shows that AVA as licensed is an effective vaccine for the protection of humans against anthrax, including inhalational anthrax, caused by any known or plausible engineered strains of *B. anthracis.*

[1] These findings and recommendations appear in *The Anthrax Vaccine: Is It Safe? Does It Work?* (Institute of Medicine, 2002; LM Joellenbeck, LL Zwanziger, JS Durch, BL Strom, eds.; Washington, D.C.: National Academy Press). The complete report is available on the Internet at http://www.nap.edu/catalog/10310.html.

Recommendations

- Additional passive protection studies with rabbits and monkeys including the transfer of animal and human sera are urgently needed to quantify the protective levels of antibody in vivo against different challenge doses of anthrax spores.
- Additional active protection studies should be conducted or supported to develop data that describe the relationship between immunity and both specific and functional quantitative antibody levels, including studies of
  - the relationship between the vaccine dose and the resulting level of antibody in the blood of test animals that protects the animals from challenge;
  - the relationship between the level of antibody that protects animals from challenge and the level of antibody present in humans vaccinated by the regimen currently recommended for the licensed product; and
  - the vaccine dose that results in a level of antibody in the blood of human volunteers similar to that in the blood of the protected animals.
- The Department of Defense should support efforts to standardize an assay for quantitation of antibody levels that can be used across laboratories carrying out research on anthrax vaccines.
- The Department of Defense should pursue or support additional research with laboratory animals on the efficacy of AVA in combination with antibiotics administered following inhalational exposure to anthrax spores. Studies should focus on establishment of an appropriate duration for antibiotic prophylaxis after vaccine administration.

CHAPTER 5

Findings

- The presence or absence of VAERS reports (or other case reports) cannot be considered in and of itself to provide adequate evidence of causal associations or its absence. Reports may suggest hypotheses for further investigation, but it must be borne in mind that many different factors beyond the presence of health symptoms can influence whether a report is filed.
- Concerns of service members that reporting to VAERS is sometimes discouraged within the military setting have been responded to appropriately with reminders to physicians that DoD policy requires submission of a VAERS report for postvaccination health events that result in hospitalization or the loss of time from duty of more than 24 hours. Additional steps, however, are possible to facilitate reporting to VAERS, including improvements in the coding of health care visits that are potentially vaccine related.
- The committee has reviewed the case materials and the methods applied by VAERS and AVEC to evaluate those materials and concurs with their conclusions that those materials present no signals of previously undescribed serious adverse reactions associated with exposure to AVA.

Recommendation

- DoD should develop and implement a system to automate the generation of VAERS reports within the military health care system, using codes to identify from automated records those health care visits that are potentially vaccine related. Use of these codes should generate an automatic filing of a VAERS report that includes the specific diagnoses for the clinical event(s) that prompted the health

care visit. However, the submission of reports to VAERS should not be restricted to visits assigned codes that identify them as potentially vaccine-related.

CHAPTER 6

Findings

- DMSS data are screened quarterly to identify statistically significant elevations in hospitalization and outpatient visit rate ratios associated with receipt of AVA. In this way, DMSS promises to be very useful as a tool for hypothesis generation.
- The elevated rates of specific diagnoses in the various analyses of DMSS data are not unexpected per se; that is, they appear to be explicable by chance alone. The bias of selection of healthy individuals for receipt of AVA is also a likely explanation for some observed associations. Thus these elevated rate ratios should not be automatically viewed as an indication of a causal association with the receipt of AVA. However, additional follow-up is needed.
- Examination of data from the DMSS database to investigate potential signals suggested by VAERS reports related to vaccination with AVA has not detected elevated risks for any of these signals for the vaccinated population, although continued monitoring is warranted.
- The data available from VAERS, DMSS, and epidemiologic studies indicate the following regarding immediate-onset health events following receipt of AVA:
  - Local events, especially redness, swelling, or nodules at the injection site, are associated with receipt of AVA, are similar to the events observed following receipt of other vaccines currently in use by adults, and are fairly common.
  - Systemic events, such as fever, malaise, and myalgia, are associated with receipt of AVA, are similar to the events observed following receipt of other vaccines currently in use by adults, but are much less common than local events.
  - Immediate-onset health effects can be severe enough in some individuals to result in brief functional impairment, but these effects are self-limited and result in no permanent health impairments.
- There is no evidence that life-threatening or permanently disabling immediate-onset adverse events occur at higher rates in individuals who have received AVA than in the general population.
- The available data from both active and passive surveillance indicate that there are sex differences in local reactions following vaccination with AVA, as there are following the administration of other vaccines. For female service members, reactions following vaccination with AVA can have a transient adverse impact on their ability to perform their duties. The factors that account for these sex differences are not known.
- The currently licensed subcutaneous route of administration of AVA and the six-dose vaccination schedule appear to be associated with a higher incidence of immediate-onset, local effects than is intramuscular administration or a vaccination schedule with fewer doses of AVA. The frequencies of immediate-onset, systemic events were low and were not affected by the route of administration.
- The available data are limited but show no convincing evidence at this time that personnel who have received AVA have elevated risks of later-onset health events.

Recommendations

- AMSA staff should follow up the currently unexplained elevations in hospitalization rate ratios for certain diagnostic categories among the cohorts of AVA recipients. Studies might include additional analyses with the database, or examination of medical records to validate and better understand the exposures and outcomes in question. A protocol should be developed to ensure that such follow-up regularly and reliably occurs after a potential signal is generated.
- Future monitoring and study of health events following vaccination(s) with AVA (and other vaccines) should continue to include separate analyses of data for men and women.
- DoD should continue to support the efforts of CDC to study the reactogenicity and immunogenicity of an alternative route of AVA administration and of a reduced number of vaccine doses.
- DoD should develop systems to enhance the capacity to monitor the occurrence of later-onset health conditions that might be associated with the receipt of any vaccine; the data reviewed by the committee do not suggest the need for special efforts of this sort for AVA.

CHAPTER 7

Findings

- FDA's process of plant inspection and FDA's validation of the vaccine manufacturing process have changed and have become more stringent with time.
- With high-priority efforts by the manufacturer and FDA, the manufacturing process for AVA has been validated so that vaccine manufactured postrenovation has been approved for release and distribution.
- AVA will now be produced by a newly validated manufacturing process under strict controls, according to current FDA requirements. As a result the postrenovation product has greater assurance of consistency than that produced at the time of original licensure.

CHAPTER 8

Findings

- Current events in both the military and the civilian arenas highlight and confirm the importance of ensuring both the availability and the quality of the nation's anthrax vaccine.
- The AVA product produced in a renovated facility by a newly validated manufacturing process could differ from the prerenovation product in terms of its reactogenicity, immunogenicity, and stability. The information available to the committee suggests that AVA lots manufactured postrenovation may show less variation in reactogenicity because of greater consistency in the production process, and there is no a priori basis to believe that the postrenovation product will be more reactogenic or less immunogenic than the older vaccine.
- Given the concerns raised by some service members about the safety of the anthrax vaccine, the creation of AVEC was an appropriate complement to other resources in FDA, the Centers for Disease Control and Prevention (CDC), and DoD for the monitoring of vaccine safety concerns. The results of the extra monitoring did not indicate the existence of any sentinel events that were not detected in the existing FDA and CDC reviews. The committee finds no scientific reason for the continued operation of AVEC in its present form.

- The possibility of detecting a signal in VAERS will be even more limited for AVA than for many other vaccines, given the relatively small population (primarily military personnel) exposed to the vaccine and the low rates at which the hypothesized health effects of greatest concern might be expected to occur in that population.
- VAERS is a critically important source of signals, that is, hypotheses about potential associations between a vaccine and a health event, but these hypotheses must be tested through other means. DMSS gives DoD a unique resource with which to conduct such testing.
- DMSS is a unique and promising population-based resource for monitoring of the emergence of both immediate-onset and later-onset (perhaps up to 5 years) health concerns among military personnel and for testing of hypothesized associations between such health concerns and exposures resulting from military service, including vaccines.
- DoD personnel have used DMSS to conduct valuable analyses in response to concerns about health effects that might be associated with vaccination with AVA. Yet, DoD personnel working with DMSS data are necessarily limited in time and focus. DMSS data could therefore yield valuable insights in the hands of civilian researchers.
- DMSS cannot be used to study mild adverse events, even if they are common.
- Because DMSS captures health care data only for military personnel on active duty, it cannot be used to study the later-onset effects of vaccines over periods of time beyond the normal length of active military service.
- The current anthrax vaccine is difficult to standardize, is incompletely characterized, and is relatively reactogenic (probably even more so because it is administered subcutaneously), and the dose schedule is long and challenging. An anthrax vaccine free of these drawbacks is needed, and such improvements are feasible.

Recommendations

- As with all vaccines, AVA lots produced postrenovation should continue to be monitored for immunogenicity and stability, and individuals receiving these lots should be monitored for possible acute or chronic events of immediate or later onset.
- DoD should disband AVEC in its current form and instead assist FDA and CDC in establishing an independent advisory committee charged with overseeing the entire process of evaluating vaccine safety. The proposed advisory committee can also assist on an ad hoc basis in the interpretation of potential signals detected in VAERS or other sources regarding the safety of any vaccine. The newly established FDA drug safety committee might be an appropriate model.
- If DoD chooses to continue AVEC, DoD should consider redefining the panel's role so that it serves as an independent advisory committee that responds on an ad hoc basis to specific requests to assist in the interpretation of potential signals detected by others (e.g., CDC and FDA) and reported to VAERS or other sources regarding the safety of all vaccines administered to service personnel rather than continuing the panel's current role of rereviewing each VAERS report related to AVA.
- DoD should develop a capability for the effective use of DMSS to regularly test hypotheses that emerge from VAERS and other sources regarding vaccine-related adverse events.
- DoD should actively support and advance the development of DMSS data resources and the staffing of units that will allow the continuing rapid and careful analysis of these data, including but not limited to the proposed collaboration between CDC and the Army Medical Surveillance Activity.

- DoD should investigate mechanisms that can be used to make DMSS data available to civilian researchers, as is done by civilian agencies, with appropriate controls and protections for privacy.
- DoD should develop ad hoc prospective cohort studies in one or more military settings to test hypotheses that emerge from VAERS, DMSS, or other sources. However, the committee does not recommend that such studies targeted at AVA be conducted at present since no convincing evidence of new adverse events in AVA recipients sufficient to merit a prospective investigation has been presented. Rather, further studies of the effects of AVA should be performed in the context of studies of the effects of all vaccines administered to members of the military.
- DoD should carefully evaluate options for longer-term follow-up of the possible health effects of vaccination against anthrax (and other service-related exposures). The committee recommends consideration of the following specific steps:
  - Encourage participation in the Millennium Cohort Study as part of a program to ensure adequate monitoring for any possible later-onset health effects that might be associated with vaccination with AVA or other service-related exposures.
  - Collaborate with the Department of Veterans Affairs (VA) to monitor service members who receive medical care through VA facilities after separation from military service. Linking of data from DMSS to data from VA is a possible tool. Even though those who receive their medical care through VA may be an unrepresentative minority of all former military personnel, valid comparisons may be possible between those within that population who received a vaccine or other exposure and those who did not.
  - Collaborate with VA to obtain fact-of-death information from the Beneficiary Identification and Records Locator System and with the Social Security Administration to obtain death files. Data on the cause of death should be obtained from the National Death Index as needed.
  - Ensure the long-term maintenance of DMSS and other relevant paper and electronic records so that retrospective studies will be feasible if health concerns are identified in the future.
- DoD should continue and further expedite its research efforts pertaining to anthrax disease, the *B. anthracis* organism, and vaccines against anthrax. Research related to anthrax should include, in particular, efforts such as the following:
  - DoD should pursue and encourage research to develop an anthrax vaccine product that can be produced more consistently and that is less reactogenic than AVA;
  - DoD should pursue and encourage research regarding the *B. anthracis* capsule;
  - DoD should pursue and encourage research on the mechanisms of action of the anthrax toxins; such research could lead to the development of small-molecule inhibitors;
  - DoD should pursue and encourage research to map the epitopes of the protective antigen that correlate with specific functional activities;
  - DoD should pursue and encourage research to test the therapeutic potential of antitoxin proteins or antibodies; and
  - DoD should pursue and encourage research into additional potential virulence factors in *B. anthracis* and into other possible vaccine candidates.