



## **CDC Anthrax Vaccine Safety & Efficacy Research Program: Interim Report**

Committee to Review the CDC Anthrax Vaccine Safety and Efficacy Research Program, Board of the Medical Follow-Up Agency

ISBN: 0-309-57987-2, 57 pages, 8 1/2 x 11, (2001)

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# CDC Anthrax Vaccine Safety & Efficacy Research Program

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**Interim Report**



INSTITUTE OF MEDICINE

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Support for this project was provided by the Centers for Disease Control and Prevention, Department of Health and Human Services (Contract No. 200–2000–00629). The views presented in this report are those of the Institute of Medicine Committee to Review the CDC Anthrax Vaccine Safety and Efficacy Research Program and are not necessarily those of the funding agencies.

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*Willing is not enough; we must do.*

—Goethe



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\*Through March 2001.

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## Contents

	<b>PREFACE</b>	<b>ix</b>
	<b>ACKNOWLEDGMENTS</b>	<b>xi</b>
	<b>EXECUTIVE SUMMARY</b>	<b>1</b>
<b>CHAPTER 1:</b>	<b>INTRODUCTION AND BACKGROUND</b>	<b>11</b>
<b>CHAPTER 2:</b>	<b>INTERIM FINDINGS AND RECOMMENDATIONS</b>	<b>21</b>
	<b>REFERENCES</b>	<b>37</b>
	<b>ACRONYMS</b>	<b>39</b>
<b>APPENDIX A:</b>	<b>STUDY ACTIVITIES</b>	<b>41</b>
<b>APPENDIX B:</b>	<b>BIOGRAPHICAL SKETCHES</b>	<b>43</b>



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## Preface

Anthrax in its inhalational form is a deadly but very rare manifestation of infection with a common organism, *Bacillus anthracis*. Anthrax spores are very stable, a characteristic that makes possible their delivery as a weapon of biological warfare, and examples of weapons development efforts using anthrax are well known. It is important to protect the men and women in our armed services to the greatest extent possible. The Department of Defense (DoD) established the Anthrax Vaccine Immunization Program (AVIP) in order to do so; however, some parties have raised questions about the safety and even the efficacy of the vaccine. As a result, the DoD is sponsoring an Institute of Medicine (IOM) study of the safety and efficacy of the vaccine, and Congress has instructed the Centers for Disease Control and Prevention (CDC) to conduct further safety and efficacy research. The CDC contracted with the IOM to review their research program for completeness and appropriateness. This document is an interim report of the Committee to Review the CDC Anthrax Vaccine Safety and Efficacy Research Program, and reflects only a preliminary review of a program still in development.

The CDC's anthrax vaccine safety and efficacy research program includes projects aimed at supporting an application to change the labeling of the licensed anthrax vaccine, specifically to change the route of administration from subcutaneous to intramuscular injection and to reduce the total number of doses. Based upon use of other vaccines and previous research, it is reasonable to expect that reduction in local and short-term systemic reactions to the presently available vaccine will be achieved by changing the route and schedule for inoculation. In addition, the CDC is also researching the acceptability of the anthrax vaccine, and so part of the research program involves assessing the knowledge, attitudes, and beliefs of vaccine recipients concerning the anthrax vaccine.

While restricted by the statement of task to an evaluation of the CDC's anthrax vaccine safety and efficacy research program using the licensed vaccine, the committee cannot help but observe the substantial opportunity for development of a different and improved anthrax vaccine product. The science of vaccinology has made great strides in methods to enhance the purity, potency and consistency of vaccines. The committee members would welcome additional emphasis, from relevant federal agencies and/or industry, on research and development toward realizing the potential of contemporary vaccinology for a new anthrax vaccine product, free from impurities, that is, essentially a pure protective antigen vaccine.

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## Acknowledgments

The committee wishes first to acknowledge the early contribution of Trudy Bush, Ph.D., M.H.S., of the University of Maryland School of Medicine. Dr. Bush's insights were greatly appreciated but cut tragically short when she was suddenly deceased in early April of 2001. She is and will continue to be sorely missed.

Many individuals assisted the committee with helpful advice and suggestions in the preparation of this interim report, and any list runs the risk of unintentional omissions.

The committee particularly thanks two consultants, Sandra Berry, Director of the Survey Research Group of RAND, and Dr. David Madigan, Professor of Statistics at Rutgers University. Dr. John C. Bailar III, M.D., Ph.D., Professor Emeritus at the University of Chicago, provided advice on multiple occasions.

The committee appreciates the support provided by the sponsor of the project, the Centers for Disease Control and Prevention (CDC) of the Department of Health and Human Services. Many individuals from the CDC were most helpful, in particular the primary contact person, Randy Louchart, as well as David Ashford, Ph.D.; Betsy Cadwell, M.S.P.H.; Jose F. Cordero, M.D., M.P.H.; Deborah Gust, Ph.D.; Laurie Kamimoto, Ph.D.; Stacy Martin; Michael M. McNeil, M.D., M.P.H.; Gina Mootrey, D.O., M.P.H.; Nina Morano; Bradley Perkins, M.D.; Robert Pless, M.D.; Conrad Quinn, Ph.D.; Benjamin Schwartz, M.D.; Kristine Sheedy, Ph.D.; Robert Jacobson; and many others.

The committee greatly appreciated the helpful information provided by Col. Arthur M. Friedlander, M.D., and LTC John D. Grabenstein, R.Ph., Ph.D., of the DoD; Vito Caserta, M.D., M.P.H., of the National Vaccine Injury Compensation Program, Health Resources and Services Administration, DHHS; Mr. Brent Jaquet, of the Office of Congressman C.W. Bill Young; and M. Miles Braun, M.D., M.P.H., Juli Clifford, and Karen Goldenthal, M.D., all of FDA.

The committee thanks members of the public who attended the April 18, 2001, joint meeting with the Committee to Assess the Safety and Efficacy of the Anthrax Vaccine and addressed the committees, including Major (ret) Sonnie Bates; Capt. John Buck, M.D.; Col. (ret) Redmond Handy; Major Jon F. Ireland; Technical Sergeant Jeffrey Moore; Ms. Nancy Rugo; Master Sergeant (ret) Thomas Starkweather; Capt. Jean Tanner; and others who spoke that day.

At the Institute of Medicine, the study director greatly appreciated the assistance of Phillip Bailey, Sue Barron, Andrea Cohen, Lois Joellenbeck, Karen Kazmerzak, Linda Kilroy,

Janice Mehler, Saira Moini, Jennifer Otten, Bronwyn Schrecker, Sally Stanfield, and Vanee Vines, among others. S.Renee Twombly helped in copy editing the report.

### 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:

**ANN M.ARVINE**, Lucile Salter Packard Professor of Pediatrics and Professor of Microbiology and Immunology, Stanford University

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**PHILIP RUSSELL**, Potomac, MD

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 Dr. F.Marc LaForce, Director, Basics II, Arlington, VA, appointed by the Institute of Medicine and Dr. Gilbert S.Omenn, appointed by the NRC's Report Review Committee, who was 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.

## Executive Summary

The Department of Defense's Anthrax Vaccine Immunization Program (AVIP) to vaccinate all troops against anthrax has become a controversial issue. On the one hand, inhalational anthrax disease has a high fatality rate, close to 100 percent, and the infectious organism, *Bacillus anthracis*, is considered to be the foremost threat for use in biological warfare. On the other hand, the anthrax vaccine and the AVIP have been subject to an unusual degree of concern from some service personnel and their families regarding possible adverse events associated with vaccination. The Congress has responded to these issues, mandating further study of the vaccine by the Department of Defense (DoD), the National Institutes of Health (NIH), and the Centers for Disease Control and Prevention (CDC), both individually and collaboratively.

The CDC contracted with the Institute of Medicine (IOM) to establish an expert panel to review the completeness and appropriateness of their research plan to study the safety and efficacy of the anthrax vaccine, and to evaluate alternative routes and schedules of administration in order to reduce adverse effects while maintaining vaccine effectiveness. The study is planned for a total duration of 24 months. This interim report sets out the committee's findings, eight months into the project. Both the committee's review and the CDC's research program are ongoing and further developments are expected. The key messages at this time reflect that interim status, and encourage further development (Box 1). In brief, the CDC's plan appears to include useful components that have not to date been integrated into a whole or comprehensive plan. No matter how meritorious the parts, however, the apparent lack of overall planning and coordination of the whole is a deficit that should be remedied. The committee could not fairly evaluate the plan for its completeness and appropriateness with respect to its goals, as long as the plan itself was not yet completely developed. Based on the information presented regarding the components developed to date, however, the committee looks forward to further review of comprehensive, and of additional detailed, information as soon as it is available.

As will be noted below, Congress explicitly called for cooperation between the CDC and the NIH and the DoD. This report is directed specifically toward the CDC's plans, and has not included any review of the overall research portfolios of the NIH and the DoD. When specific areas of potential coordination were apparent, the committee highlighted them, but the committee also assumes that other areas of coordination could emerge in the course of collaborative discussions.

Finally, the committee also strove to distinguish overall program review from detailed and technical advice on specific protocols. The committee's assessment was that both sorts of advice could be useful to the CDC, but that sources other than IOM should be consulted for the latter. The committee's general recommendations, in [Box 2](#) below, reflect these overall findings.

#### **BOX 1 KEY FINDINGS OF INTERIM REPORT**

- 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.

#### **BOX 2 GENERAL RECOMMENDATIONS FOR CDC'S ANTHRAX VACCINE RESEARCH PROGRAM**

##### **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).

Congress has laid out the elements of the CDC's research mandate, namely, to study the safety and efficacy of anthrax vaccine by addressing: (1) risk factors for adverse reactions, including gender differences; (2) determining immunologic 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. Congress separately mandated that the DoD enter into a contract with the Institute of Medicine for a study aimed at review of currently existing data on the safety and efficacy of the licensed vaccine (see [Figure 1](#)). The two contracts were independent and the charges distinct although related. In order to facilitate coordination, the committees share staff and include several members who serve on both committees.

The CDC's research program addresses the safety and efficacy of the licensed anthrax vaccine (anthrax vaccine adsorbed, or AVA), using a multi-faceted approach located in two distinct parts of the agency, the National Center for Infectious Diseases (NCID) and the National Immunization Program (NIP) (see [Box 3](#)). The CDC's research plans include studies directed toward regulatory requirements for changing the labeling of the current AVA product, and other studies apparently designed with a view to furthering scientific understanding more generally. Those goals are not inconsistent, but a comprehensive plan should describe their integration. The NCID research projects primarily address the dosing schedule, route of administration, and reactogenicity of the vaccine. The NIP research projects are concerned with tracking vaccine adverse events and evaluating perceptual factors that influence vaccine acceptability; the effects of educational efforts on the knowledge, attitudes, and beliefs (KAB) of service personnel about the anthrax vaccine will also be studied.

### BOX 3 PROJECTS PRESENTED TO DATE IN CDC RESEARCH PROGRAM

#### NCID—in development

Part A: Anthrax Vaccine Adsorbed (AVA): A human reactogenicity and immunogenicity trial to address change in route of administration and dose reduction  
Part B: Non-human primate AVA dose-ranging, immunogenicity and challenge trial  
Part C: Anthrax pathogenesis, immunology, and correlates of protection against inhalational anthrax  
Human leukocyte antigen sub-study

#### NIP—in development or planned for development

Survey of knowledge, attitudes and beliefs (KAB) prevalent among military service personnel and also of military health care providers regarding the anthrax vaccine  
Survey of the KAB prevalent among military health care providers regarding practices of reporting to Vaccine Adverse Event Reporting System (VAERS)  
Data-mining in the VAERS database  
SF-36 Survey of clinical trial participants  
Hormonal correlates of adverse events in female clinical trial participants  
Long-term follow-up of any available previously immunized populations  
Meta-analysis of safety and efficacy studies on the anthrax vaccine



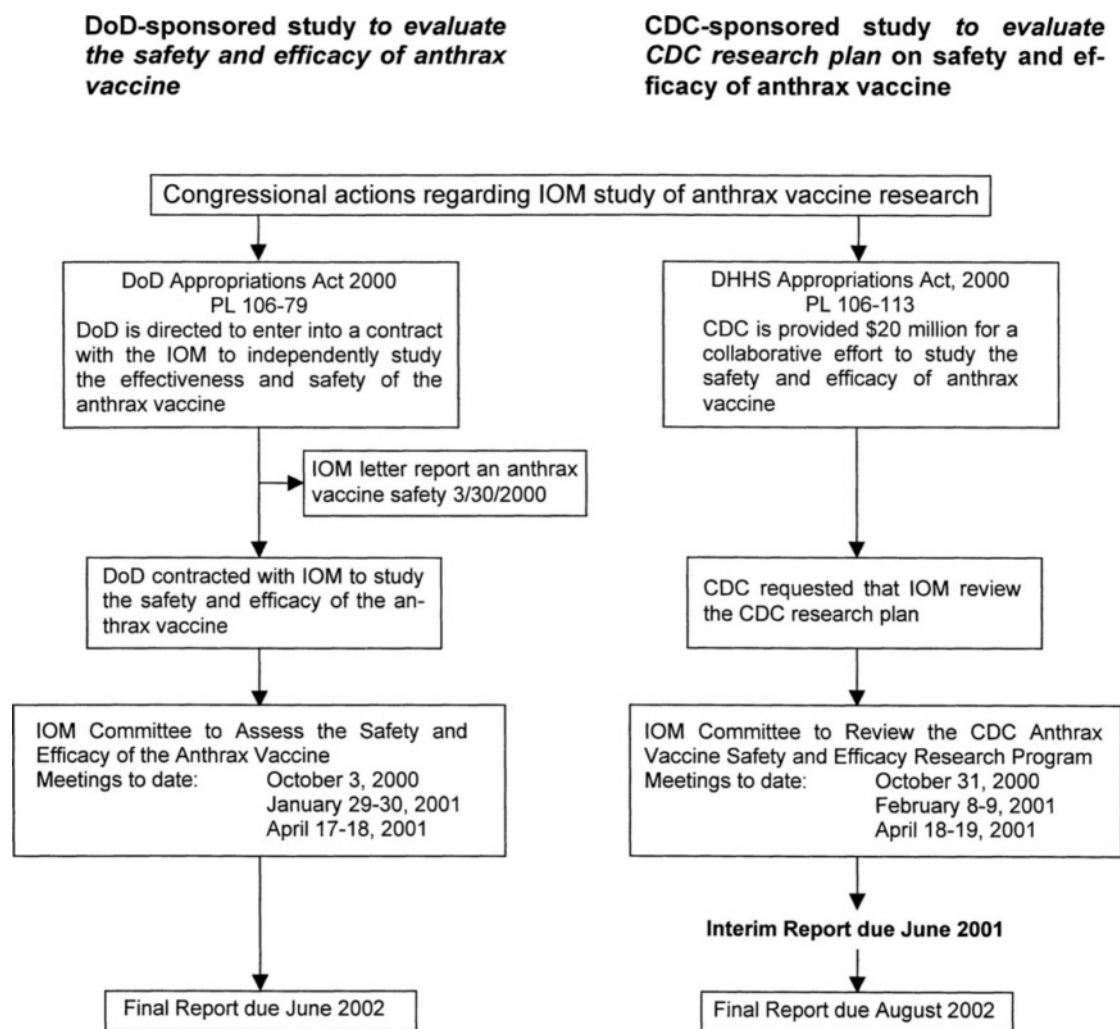


FIGURE 1 Origins of IOM Activities Related to the Anthrax Vaccine

## PROJECT-SPECIFIC FINDINGS AND RECOMMENDATIONS

### NCID-Directed Projects in the Research Program

The NCID research plans include a human clinical trial to evaluate changing the route of injection of the licensed vaccine AVA from subcutaneous to intramuscular, and reducing the total number of injections. The results of this work may be used to support a labeling change for the licensed product. Other NCID projects support and extend this work using animal trials and laboratory tests.

### Human Clinical Trial, or Part A

The human clinical trial would compare the effects of intramuscular administration with the currently recommended subcutaneous injection of the anthrax vaccine and of reducing the total number of doses. The trial will last three and a half to four years, and enrollment plans call for a total of 1300 participants from five study sites.

The committee found that the proposed research on changing the route of administration of the vaccine and reducing the number of doses required is appropriate. This trial is also necessary from a regulatory perspective in order to change the vaccine product labeling so that the military could change its practice and remain in accord with guidelines of the Food and Drug Administration (FDA). The committee considers some potential modifications, particularly to one study group, of the human clinical trial as perhaps advantageous, while recognizing that it may be difficult to implement any further changes at this date.

- **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 has not yet seen the methods section of the human clinical trial protocol, notably the specific types of statistical analyses that will be employed in the analysis of clinical trial data. The committee is concerned about the methods to be used.

- **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 notes also that the human clinical trials are intended to investigate gender differences related to adverse reactions, specifically mentioned in the Congressional mandate. Previous work (Pittman et al., submitted for publication) has shown a significantly higher frequency, and greater extent, of local adverse reactions to the anthrax vaccine when administered to women subcutaneously. The CDC plan for recruitment of volunteers anticipates a sufficient number of female subjects, 20 percent of total enrollment, to detect a difference of similar magnitude to that reported by Pittman, but not for a smaller difference. The CDC also plans a substudy of hormonal status that would further subdivide the female volunteers, so that the study would require a still larger number. As planned, the clinical trial would be powered adequately to detect a substantial difference related to sex (a biological parameter) or gender (a psychological and/or social phenomenon) in the rate of adverse reactions to subcutaneous inoculation, given successful recruitment of female subjects. However, several factors may complicate such recruitment. Belief among potential recipients that women may suffer more reactions (also indicated by the Pittman study), and plans for recruiting study volunteers from, among other groups, first responders (traditionally professions employing more men than women), together cause the committee to doubt the likelihood of enrolling female volunteers in sufficient numbers to provide adequate power for the planned studies. As planned, this study will not have adequate power to address aspects of sex or gender differences beyond route of administration.

- **The committee recommends that the CDC consider, in addition to the proposed clinical trial, a 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.**

According to presentations made to the committee and subsequent inquiries by staff members, the DMSS already collects relevant data on all medical visits in the military health care system, as well as data on anthrax vaccinations. The DMSS would thus be able to provide information on the date and ICD-9 code for visits within a given time frame following a visit for anthrax immunizations. Sex or gender difference is just one of several important items of information that could be investigated.

### **Animal dose ranging and challenge studies, or Part B**

The animal studies would compare different doses of vaccine to establish the appropriate dose for the rhesus macaque, the animal species of interest, and the effect of reducing the number of doses on the animals' circulating antibody and their ability to survive challenge with aerosolized *B. anthracis*.

The committee found that supporting animal studies are of great importance in an anthrax vaccine safety and efficacy research program. It is not possible to do a human clinical trial of vaccine efficacy for inhalational anthrax: the disease has a high fatality rate, and improved working conditions in goat hair and woolen mills, and use of synthetic materials, have (fortunately) eliminated the major sources of naturally occurring cases in the United States. As a model for effects in humans, animals that can develop inhalational anthrax, rhesus macaques, will be immunized using different regimens. In earlier trials, however, the macaques received the same dose as a human would, resulting in more vaccine per unit body weight than a human would receive. The CDC plans to do a dose-ranging study to establish the appropriate dose of vaccine for a rhesus macaque as a basis for future studies. The criteria for the choice of an appropriate dose have not been defined to date. The animals will be immunized with different dilutions of vaccine, after which their immune systems will be challenged by exposing them to a standard dose of aerosolized *B. anthracis* spores, to determine whether they have developed protection against infection.

Often such a series of dose-ranging and challenge studies would be preceded by a passive antibody transfer study, in which antibody-containing serum from immunized humans is given to the animals so that they have passive immunity (that is, they have received antibodies but do not actively make their own antibodies because they have not been vaccinated). Then animals that have been given different amounts of the human antibodies would be challenged to help establish what blood concentration of antibodies is necessary for protection. The CDC's plans do not currently include a study to demonstrate passive transfer of human serum antibody to macaques and determine the level of antibody necessary for protection. The committee believes that this omission should be addressed.

Furthermore, the dose-ranging study the CDC plans to do would use a series of dilutions where the differences between dilution steps are large. The proposed series starts with a dilution of 1:5, then proceeds with 1:2 dilutions, so the series is 1:5, 1:10, 1:20, etc. The committee remains concerned that important information may be unobserved because of the differences

between dilutions and recommends using a dilution series that would be two-fold from the first step: 1:2, 1:4, 1:8, etc.

- **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.**

### **Assays addressing correlates of immunity, or Part C**

The CDC plans a series of assays to establish expected levels of antibodies and other immune system responses, such as proliferation of specific cell types in the systems of immunized humans and animals. The committee found that the scientific account of immune correlates has developed rapidly and commendably in the case of the plans for most of the assays with some exceptions. As an example of such an exception, the CDC proposes to use microarray technology to assess whole-cell gene expression in response to vaccination or challenge. The CDC noted at the time of presentation that the technical proposal for use of this assay was still in development; indeed, at that time the rationale for the use of microarrays was not yet clear to the committee.

- **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.**

### **Human Leukocyte Antigen (HLA) substudy**

The CDC plans a substudy to evaluate the relation if any between HLA subtypes and the development of immunity following immunization against anthrax. The committee found that the rationale for the HLA substudy was not yet completely described and recommends further explanation of its role if it is to be part of the CDC's research program.

### **NIP-Directed Projects of the Research Program**

The NIP has proposed studies that are quite varied in technique and rationale and, at the time of writing the interim report, also varied widely in level of development. The committee kept in mind the preliminary nature of some of the proposals while assessing the program. Perhaps the most fully developed projects are studies intended to assess knowledge, attitudes, and beliefs (KAB) of service personnel about the anthrax vaccine, or of health care providers about the system for reporting adverse events occurring after a vaccination. The NIP is planning other studies as well, as mentioned later.

### **Survey of knowledge, attitudes, and beliefs of military personnel about the anthrax vaccine**

This survey will be designed to assess the knowledge, attitudes, and beliefs of military service members about the anthrax vaccine, and will be followed with a second survey after a period of two to three years to assess change in knowledge, attitudes, and beliefs. The committee found that the rationale for investigating the KAB of service personnel was appropriate. The committee also found, however, that the plans for the study may be compressed more than warranted. The study plans now call for, first, the use of military personnel focus groups to design a survey, then the administration of the survey, then the provision of such educational materials as the survey results indicate may be needed, and finally the administration of the survey a second time to a second group of military personnel. The committee suggests that if the

investigators were to invest more in the design phase of the study, not only with focus groups but also a pilot survey and perhaps cognitive and psychometric tests of the potential educational materials, they would then be in a position to design a better targeted survey and to make more informed determinations of parameters such as sample size.

In public hearings, the committee heard from military service members outside the health care system about their perceptions of the military health care system. Because of the special role of health care providers in informing people and the influence they have on the KAB of their patients, the committee suggested that health care providers be studied separately about their KAB regarding AVA and the AVIP. Such a separate study might be combined with another planned survey of health care providers (see below). Additionally, both surveys—or perhaps even a third, specifically directed survey—might profitably be designed to generate important information about perceptions of the military health care system per se. Concerns about the AVIP, and the use of civilian as well as military health care facilities, may have effects on the KAB of military personnel, as the military may be perceived by some service personnel (however unfairly) as taking a less direct interest in the health of its troops. That perception then might affect the confidence and trust of military patients in their health care providers and the military health care system.

- **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.**

#### **Survey of knowledge, attitudes, and beliefs of military vaccinee providers about VAERS reporting**

The national passive surveillance system for medical events occurring after administration of United States licensed vaccines is called the Vaccine Adverse Event Reporting System (VAERS). The VAERS depends on spontaneous voluntary reporting, and like any such system, the VAERS typically receives fewer reports than the actual number of adverse reactions that occur. In the case of the anthrax vaccine, however, some service members and other concerned individuals suspect that the difference may be particularly great, possibly due to aspects of military culture in general or the AVIP in particular that may tend to discourage reporting to VAERS. This survey will be designed to assess the knowledge, attitudes, and beliefs of military and civilian health care providers regarding VAERS reporting, and will be followed with a second survey after a period to be determined to assess change in knowledge, attitudes, and beliefs.

The committee found that the rationale for investigating the KAB of military vaccine providers toward VAERS reporting was appropriate, but cautioned that this activity together with associated educational interventions could affect the rate of VAERS reporting. Ongoing monitoring of VAERS reports on the anthrax vaccine therefore should be checked with an independent source of information about adverse events, and both systems compared to reports of adverse events about comparable vaccines. The committee suggests that data from the Defense Medical Surveillance System (DMSS), which tracks the medical encounters and other pertinent data on military personnel, might offer a source for such independent comparisons, and noted further that this is an example of an area of potential collaboration between the CDC and the DoD.

Further, the committee found that the survey of military vaccine providers regarding VAERS might be coupled with the segment of the survey discussed above, i.e., the KAB of health care providers about the anthrax vaccine. Thus, the survey discussed here could be expanded to assess the KAB of health care providers regarding both VAERS reporting and the anthrax vaccine and perhaps other vaccines. Finally, the committee found that extensive previous research on VAERS reporting might justify reconsideration of the sample size, perhaps allowing a reduction in the number of subjects.

- **The committee recommends that the CDC consider expanding the design phase of the knowledge, attitudes, and beliefs (KAB) study of military vaccine providers regarding the Vaccine Adverse Event Reporting System (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 knowledge, attitudes and beliefs (KAB) of health care providers regarding the anthrax vaccine in the study now designed to assess only KAB on the Vaccine Adverse Event Reporting System (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 Defense Medical Surveillance System (DMSS), when assessing any monitoring of, or modification to, Vaccine Adverse Event Reporting System (VAERS) reporting practices and VAERS analyses.**

### **CDC proposal for use of the Short Form 36**

The NIP proposes to add to the human clinical trial an application of the Short Form 36 (SF-36) to evaluate changes in self-reported health status over the course of the human clinical trial. The SF-36 is a very well developed survey instrument for assessing general perceptions of the respondents' own health.

The committee found that the rationale for including in the human clinical trial a self-assessment of health status using the SF-36 was appropriate. However, the SF-36 can be augmented by existing, validated items to address populations more specifically.

- **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.**

### **Remaining components of the research program directed by the NIP**

The committee found that the remaining components of the segment of the CDC's research program under the purview of the NIP were not developed in detail sufficient for assessment. These components include data-mining in the VAERS database, hormonal correlates of adverse events in women, long term follow-up of populations immunized at least twenty years previously, and meta-analysis of studies on the safety and efficacy of the anthrax vaccine. The committee has not made specific recommendations on these projects, as they are still early in development.

The committee's recommendations for the interim are listed in [Box 4](#). The committee looks forward to receiving further information and protocols as the CDC continues to develop its overall anthrax vaccine safety and efficacy research program.

#### BOX 4 COLLECTED RECOMMENDATIONS

##### 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).

##### 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.

# 1

## Introduction and Background

Anthrax is a disease caused by a common and widespread organism. *Bacillus anthracis*, whose characteristics make it a feasible choice for biological warfare; examples of weapons development programs using *B. anthracis* are well known. Because of the potential that biological weapons using *B. anthracis* might be directed against the United States military, on May 18, 1998, the Department of Defense (DoD) ordered all service personnel to be fully vaccinated for protection against anthrax (the Anthrax Vaccine Immunization Program, AVIP). Limited availability of the anthrax vaccine forced at least a temporary slow-down in attaining this goal. But in addition to supply problems, the anthrax vaccine and AVIP have also been the subject of an unusual degree of concern from service personnel, regarding possible adverse events associated with the vaccine.

Because of the importance of protecting service personnel against biological warfare using *B. anthracis*, and because of concern among troops and their families about adverse events possibly associated with the anthrax vaccine, the Congress has also been interested in the policy and its justification and ramifications. The DoD and the Centers for Disease Control and Prevention (CDC) were directed to undertake additional research on the vaccine, both individually and collaboratively.

The CDC contracted with the Institute of Medicine (IOM) to establish an expert panel to review the completeness and appropriateness of the CDC plan for responding to the congressional mandate that CDC conduct research on the safety and efficacy of anthrax vaccine. The committee's Statement of Task (Box 1-1) reflects the congressional appropriations language (which became the Department of Health and Human Services Appropriations Act of 2000, now Public Law 106-113) almost exactly, as comparison with Box 1-2 shows. Congress directed the CDC and the NIH and DoD to collaborate and cooperate fully in this effort. Meanwhile, the DoD received congressional direction in the DoD Appropriations Act of 2000, now Public Law 106-79, whose conference report language called for study of technical matters regarding the safety and efficacy of the licensed anthrax vaccine. DoD therefore also contracted with the IOM for a separate study (see Box 1-3 for that committee's Statement of Task). The DoD-sponsored study is aimed at currently existing data on the safety and efficacy of the currently administered vaccine. The CDC-sponsored study was intended as a review of the CDC's plans for further research into the safety, effectiveness, and acceptability of the anthrax vaccine. The CDC-



sponsored study contract also called for this interim report. The full study is planned for a total duration of 24 months. This interim report sets out the committee's findings, eight months into the project. Both the committee's review and the CDC's research program are ongoing, and further developments are expected.

**BOX 1-1 STATEMENT OF TASK: COMMITTEE TO REVIEW THE CDC ANTHRAX VACCINE SAFETY AND EFFICACY RESEARCH PROGRAM**

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.

**BOX 1-2 CONGRESSIONAL LANGUAGE REGARDING 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 shall 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."*

This excerpt of PL 106-113 is the language that formed the basis of the contract for this project. In the succeeding year, however, Congress made additional comment as follows in the House-Senate conference report that was generated during fiscal year 2001 appropriations legislation, with fiscal year 2001 funding finally 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. The Network will facilitate data collection, standardization of the anthrax immunization, training and general data collection for this project."*

**BOX 1-3 STATEMENT OF TASK: DOD-SPONSORED COMMITTEE TO ASSESS THE SAFETY AND EFFICACY OF THE ANTHRAX VACCINE**

The committee will analyze available information, hold workshops, and make specific recommendations on technical aspects regarding the safety and efficacy of the licensed anthrax vaccine. The issues include the types and severity of adverse reactions, including gender differences; long-term health implications; inhalational efficacy of the vaccine against all known anthrax strains; correlation of animal models to safety and effectiveness in humans; validation of the manufacturing process focusing on, but not limited to discrepancies identified by the Food and Drug Administration in February 1998; definition of vaccine components in terms of the protective antigen and other bacterial products and constituents; and identification of gaps in existing research.

**ANTHRAX DISEASE AND PREVENTION**

**Anthrax Disease**

Anthrax disease is caused by an infection with *Bacillus anthracis* (Brachman and Friedlander, 1999; Dixon, 1999). The endospores of *B. anthracis* remain dormant in soil and are very resistant to physical and chemical conditions like heat, dryness, and disinfectants to which many organisms are susceptible. This hardiness is one characteristic that makes the organism practical as a weapons component (Inglesby, 1999; Zilinskas, 1997). *B. anthracis* can cause cutaneous, gastrointestinal, or inhalational anthrax disease, depending on the route of entry into the body (Brachman and Friedlander, 1999). Grazing animals can become infected and, in turn, can infect humans, but transmission of inhalational anthrax between human beings has not been documented. Cutaneous anthrax is generally associated with handling infected animals or their products, and is manifested as lesions that form vesicles and finally ulcers marked by a characteristic black eschar. Patients can be treated with antibiotics, and the survival rate is then over 95%. Gastrointestinal anthrax can be caused by eating infected meat. The fatality rate is variable, estimated at 25 to 75%. Inhalational anthrax is usually, if not always, fatal, even with aggressive treatment, within a matter of days after onset of symptoms (Brachman and Friedlander, 1999). Inhalational anthrax is the primary focus of the current United States military immunization program because this disease manifestation is of interest as a possible outcome of biological warfare. Inhalational anthrax depends on aerosolization of the endospores, which does not normally occur in nature but can happen under industrial conditions (as in goat hair, wool and hide processing plants) or by means of weapons.

*B. anthracis* infection and pathogenesis begin with the introduction of endospores through abrasions in the skin, or by ingestion or inhalation. The endospores then are phagocytosed by macrophages, wherein they germinate and are released as vegetative bacilli, which multiply in lymph nodes and then may enter the blood stream in great numbers, causing massive septicemia. The latter condition is more likely in inhalational anthrax than in the other forms. The virulence of the anthrax bacilli depends on expression of both bacterial capsule and toxins, the genes for which are carried on two plasmids. The loss of either the plasmid bearing the genes for the toxins, or the capsule gene plasmid, attenuates the bacterium such that it becomes unable to cause disease. It is the effects of those toxins that actually cause human disease, but the capsule inhibits the phagocytosis of vegetative bacteria. The plasmid carrying the toxin genes actually codes for three distinct proteins: protective antigen (PA), edema factor (EF), and lethal factor (LF). These factors then combine to form two toxins, each with an active domain and a binding

domain. The toxins are edema toxin, comprising PA and EF, and lethal toxin, composed of PA and LF. In both cases, PA seems to mediate binding of the toxin to the target cell and its translation to the cell's interior. The edema toxin includes an adenylate cyclase, which causes increased levels of cAMP and interferes with the cell's water balance, resulting in edema. The lethal toxin includes a protease that stimulates the release from macrophages of tumor necrosis factor  $\alpha$  and interleukin-1, which along with other cytokines may be the specific effect of lethal toxin in mortality (Brachman and Friedlander, 1999; Dixon, 1999; Little and Ivins, 1999).

### Anthrax Vaccine

Anthrax is among the first diseases for which the protective efficacy of vaccination was evaluated (Turnbull, 1991). The human efficacy data for the currently licensed vaccine comes from a field study of a similar vaccine in mill workers (Brachman et al., 1962, and see Friedlander, et al., 1999 for review). The study (which was randomized and placebo-controlled) was conducted among the workers in four northeastern United States mills that were engaged in the processing of raw goat hair. Cutaneous anthrax was a problem in the mills, and the results of the study showed 92.5% protection against cutaneous anthrax among vaccinees (gastrointestinal anthrax was not a problem in the mills, and the number of cases of inhalational anthrax was too small to serve as evidence for or against vaccine efficacy). That vaccine has been shown to be effective in protecting animals from aerosolized *B. anthracis* anthrax spores.

The licensed anthrax vaccine is a sterile filtrate, the major active ingredient being PA, from cultures of an avirulent, non-encapsulated strain of *B. anthracis*. The V770-NPI-R strain of anthrax bacilli is grown in a chemically defined culture medium. The whole bacteria in the culture are removed by filtration from the culture medium. The antigen is then adsorbed onto aluminum hydroxide, and the product is called Anthrax Vaccine Adsorbed, or AVA. The current vaccine differs slightly from the initial field trial tested vaccine in that it starts with a different avirulent strain cultured under different conditions, and uses a different aluminum preparation (Myers, presentation, 2001). There have been no randomized placebo-controlled clinical trials of the efficacy of this vaccine, but its protective efficacy has been demonstrated in several animal species. AVA is not at this time being produced, but is licensed to be manufactured by Bioport Corporation of Michigan. (Bioport, 1999).

The composition of the filtrate includes PA, possibly with traces of lethal toxin (and perhaps previously edema toxin, as mentioned in Brachman and Friedlander, 1999, though not according to recent company information) and other materials. The amount of protective antigen and other proteins per 0.5 ml dose is variable, approximately 50 micrograms of protein, of which 10 to 20 micrograms are PA, per dose (Bioport, presentation, 2001). The vaccine contains no more than 0.83 mg of aluminum per dose, 0.0025% benzethonium chloride as a preservative, and formaldehyde in final concentration not to exceed 0.02%. The potency and safety of the product comply with Food and Drug Administration (FDA) regulations. The content (purity) of PA averaged 50% with a standard deviation of 7%. Some data suggest that immunity is largely, if not entirely, a response to PA (On relevance of PA, see, for example, Gladstone, 1946; Dixon et al., 1999; Little and Ivins, 1999; and on aluminum hydroxide as an adjuvant, see for example, Wright et al., 1954, 1962; Ivins et al., 1995).

Modification of the current dosage and route of administration for the licensed product might improve its acceptability. AVA is given subcutaneously, a route that is typically associated with greater reactogenicity relative to intramuscular administration (ACIP, 1994). AVA is an unusual vaccine product because it is the only licensed vaccine to include aluminum hydroxide and to be labeled for subcutaneous administration. The immunization schedule of multiple doses and

boosters that is currently specified in the package insert was based on the number of immunizations found to afford protection against cutaneous anthrax in the field study by Brachman et al. (1962), and this inoculation schedule was not evaluated against other possible schedules. The dosage schedule is currently a 0.5 ml injection at 0, 2, and 4 weeks, again at 6, 12 and 18 months, and annually thereafter. The number of inoculations alone can be objectionable to some vaccinees.

### VACCINE RELATED ADVERSE EVENTS

Adverse events following immunization with the licensed vaccine include local and systemic reactions. The most common local reactions are erythema (redness), subcutaneous nodules at the site of injection, and less commonly, forearm swelling due to edema. Frequent systemic reactions include malaise and lassitude, and less commonly fever and chills.

Such local and short term systemic reactions are common to a number of different bacterial vaccines in current routine use. The standard regulatory terms for any undesirable effect of a vaccine (or other biologic or drug) are *adverse event* or *adverse reaction*. Adverse events can range from mild to serious or life threatening. The standard term used by regulatory agencies to describe the characteristic profile of a product and its associated adverse events is the *safety* of the product. We have used the term “adverse events” wherever possible, as “safety” may seem to over-emphasize serious or life threatening events.

The primary means of learning of adverse events associated with any licensed vaccine is the Vaccine Adverse Event Reporting System (VAERS), administered by the CDC and the Food and Drug Administration (FDA). VAERS collects and analyzes information from reports of possible adverse events following immunization (<http://www.vaers.org>, accessed 8/29/00). The VAERS program encourages reporting of any clinically significant adverse event following any immunization, and anyone can file a report to VAERS. VAERS is a passive surveillance system—it accepts reports but does not actively seek out vaccinees or health care providers to make inquiries—and as with any such system, it is safe to presume that the rate of reporting is low relative to the rate of events (though it is difficult to estimate *how* low), and varies due to the rate of events but also due to other factors such as awareness of alleged problems with a particular vaccine (Singleton et al., 1999). Between January 1990 and August 2000, 1544 reports of adverse events following administration of the anthrax vaccine were filed with VAERS. During that time period, 1,859,500 doses were given to 463,000 people (Mootrey, presentation, 10/31/00). VAERS is not designed to track the absolute rate of adverse events experienced per a given number of doses administered. Rather it is a signal-capturing or hypothesis-generating system: for example, if VAERS should receive a significant increase in reports of adverse events associated with some particular product, then that serves as a signal to investigate possible causes such as perhaps a particular lot or batch of the product that might be unusually reactogenic (see also Tilson, 1992). In the special case of the anthrax vaccine, the VAERS reports receive individual review by an independent civilian committee of medical experts, the Anthrax Vaccine Expert Committee (AVEC), which considers causality and forwards conclusions to the DoD. The AVEC had reviewed some 1530 reports as of March 15, 2001, but their first report has not yet been published (Caserta, presentation, 2000; personal communication; and <http://www.anthrax.osd.mil>, accessed 4/6/01).

## POLICY CONTEXT OF REPORT

Beginning in 1970 and continuing through today, the licensed anthrax vaccine has been routinely administered to United States workers with occupational exposure to anthrax bacteria or spores. Although human anthrax due to contact with infected animals or their products remains a health problem in some areas, currently in the United States the licensed anthrax vaccine is in use primarily by the military to protect troops from weaponized anthrax (Brachman and Friedlander, 1999; Mazzuchi et al., 2000). In 1979, an outbreak of human anthrax occurred in Sverdlovsk, U.S.S.R. (Abramova et al., 1993; Meselson et al., 1994; Jackson et al., 1998). Although initially it was officially blamed on consumption of contaminated meat, subsequent investigations of a series of cases showed pathologic lesions diagnostic of inhalational anthrax (Abramova et al., 1993), which is now admitted by the Russian government. The admission that Iraq had produced weapons containing anthrax spores during the 1991 Gulf War confirmed fears of the potential use of anthrax as a biological weapon (Zilinskas, 1997). Approximately 268,000 doses of the vaccine were distributed to troops in 1990 (IOM, 2000b).

### Anthrax Vaccination Policy

Secretary of Defense William Cohen decided in late 1997 to proceed with a plan to vaccinate all United States service members against anthrax, and immunizations began in 1998. By March 15, 2001, 2.1 million doses of anthrax vaccine had been administered to approximately 505,000 military personnel (<http://www.anthrax.osd.mil>, accessed 4/6/01). The DoD's AVIP has had, and continues to have, many formidable difficulties to manage. The licensed anthrax vaccine was only produced by one company, which is not in itself unusual, but the facility changed hands in 1998 and the company, now called BioPort, has had difficulty meeting regulatory requirements for good manufacturing practices. In fact, the product has not been manufactured since the winter of 1997. The DoD has been able to continue immunizations in spite of the limited supply of vaccine, but not at the rate first planned. In July 2000, then more officially in November 2000, the DoD slowed dramatically its immunization program, focusing only on troops thought to be at greatest potential risk (<http://www.anthrax.osd.mil>, accessed 9/5/00; Marshall, 2000).

In addition to supply problems, some vaccinees have objected to the immunization policy. There have been, for example, complaints among Gulf War veterans of chronic multisystem clinical conditions that still lack definable relationship to anthrax vaccine and to other events in the Gulf War experience (for further information on Gulf War experience and concerns, see, for example, Presidential Advisory Committee, 1996; Iowa Persian Gulf Study Group, 1997; Fukuda et al., 1998; Hotopf et al., 2000; IOM, 1996, 2000a, 2000b). Even though there is no definable relationship of anthrax vaccine to illnesses of long-term late appearance or duration, there has been a perception in a small minority of military personnel that the anthrax vaccine is dangerous.

The AVIP, and the anthrax vaccine itself, have become a focal point of great concern on the part of at least a segment of the military and interested public. The Congress has responded to that concern, and several hearings have been held by relevant committees. The Congress also appropriated funds to the DoD and to the CDC for the further study of the anthrax vaccine (see [Figure 1](#)).

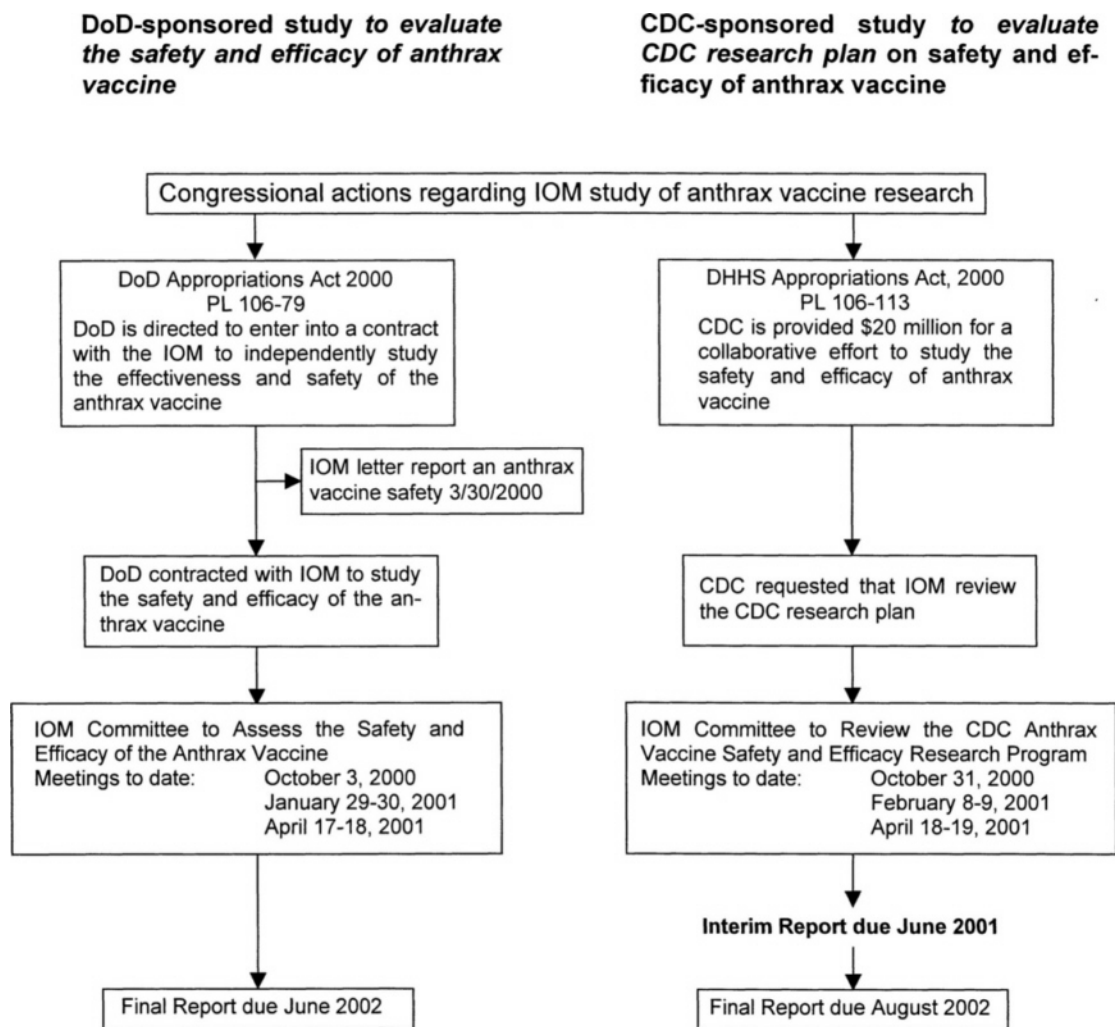


FIGURE 1 Origins of IOM Activities Related to the Anthrax Vaccine

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## CDC'S REPONSE TO CONGRESS

The CDC intends to comply with the congressional mandate to study adverse events and the efficacy of the anthrax vaccine by conducting various activities including studies by two of its subsidiary units, the National Center for Infectious Disease (NCID) and the National Immunization Program (NIP). The CDC's research program addresses various and interwoven aspects of the licensed anthrax vaccine (anthrax vaccine adsorbed, or AVA) on a variety of levels. On the level of the immunological properties of the vaccine, for example, the CDC plans include studies to determine the amount of specific types of antibodies produced in response to immunization. On the level of the medical symptoms that some vaccinees may experience, and that may influence acceptability of the vaccine, the CDC plans include studies of the effects of different routes of administration on the frequency and extent of such adverse reactions. On the level of perceptual factors that affect the acceptability of a vaccine, the CDC plans include a survey to assess service members' knowledge, attitudes, and beliefs about the anthrax vaccine.

NCID's projects to identify risk factors and improve use of the vaccine itself are also very relevant to the vaccine's adverse event profile. The NCID's effort is the investigation of vaccine immunogenicity and effectiveness, while the NIP concentrates on vaccine adverse events and acceptability. The NCID, in collaboration with the DoD-USAMRIID, issued a three-part request for proposals for studies addressing the dosage, route of administration, and immunologic correlates of protection of the AVA. The acceptability of the vaccine would improve, and acute local reactions would likely decrease, if it could be administered intramuscularly and if fewer doses were required. Recent data suggest that these changes may be possible (Pittman et al., submitted for publication), and the NCID studies are designed to further evaluate these changes. If the studies support the reduction in doses or change in route of administration, then the results could support a supplementary application to change the labeling of the AVA product.

Although the FDA does not regulate medical practice, and specifically does not oversee whether health care providers prescribe regulated products according to the directions in the product labeling, the administration of medical products by the United States military is a special situation. The Gulf War was the occasion of issuance of special rules that allowed the administration of investigational products, such as pyridostigmine bromide, for specific wartime indications, as deemed necessary to protect troops from chemical or biological weapons (note, however, that while the anthrax vaccine was administered during the Gulf War, it was a licensed, not investigational, vaccine). The intervening decade has seen a great deal of policy and regulations development related to the use of new medical products in the military (see Raub, 1999, and FDA, 1999). In general, the military is not in a position to adopt a policy endorsing uses of drugs or vaccines in ways other than directed in the FDA-approved product labeling. Any such usage is called "off-label" use. Concern in the FDA (and the DoD) about officially sanctioned off-label use of medical products was underscored in a letter in response to unspecified reports of off-label anthrax vaccine administration, from Dr. Katherine Zoon, Director of FDA's Center for Biologics Evaluation and Research to Dr. Sue Bailey, Assistant Secretary of Defense for Health Affairs (Zoon, 1999). In sum, in order for the DoD to administer the anthrax vaccine by a different route or with a reduction in total doses, it is first necessary that the product labeling be formally changed.

The NIP is, as noted, concerned with tracking vaccine adverse events and improving vaccine acceptability. In order to assess the vaccine adverse event profile, the NIP hopes to improve the detection of true adverse events, and in order to improve vaccine acceptability, the NIP hopes to

improve education and communication about the vaccine, and confidence among vaccinees that adverse events will be registered and prevented or treated.

The plans of the NIP to improve the adverse event profile and the acceptability of the vaccine include research and programmatic components, with only the former (research) to be addressed in this interim report. As part of the research effort, the NIP will be conducting focus groups and knowledge, attitudes, and beliefs (KAB) surveys among military personnel who have or will receive the anthrax vaccine, with a view to improving education and communications. The NIP is also proposing to study KAB among health care providers about VAERS reporting. The NIP is working to develop strategies and techniques for more complete analysis of the data (“data-mining”) in VAERS as well. In addition, the NIP is working on several other projects in support of the NCID-directed human clinical trials.



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## 2

### Interim Findings and Recommendations

This chapter presents the interim findings of the committee, eight months into a 24-month study, regarding the Centers for Disease Control and Prevention (CDC) research program on the anthrax vaccine. Within the CDC, the research activities related to the anthrax vaccine have been under the purview of two parts of the agency, the National Center for Infectious Diseases (NCID) and the National Immunization Program (NIP).

As was mentioned in the previous chapter, the committee was charged with advising the CDC on the completeness and appropriateness of the agency's plan to study the safety and efficacy of anthrax vaccine, addressing the following aspects of the Congressional mandate: risk factors for adverse reactions, including gender differences; the determination of immunologic correlates of protection and documentation of vaccine efficacy; and optimization of the vaccination schedule and routes of administration to assure efficacy while minimizing the number of doses required and the occurrence of adverse events. Also as described previously, the anthrax vaccine and the Department of Defense (DoD) policy decision of universal vaccination for troops have been associated with concern among some military personnel and their families. The dissatisfaction could result from various combinations of factors, including potential for local or systemic adverse events, the number and timing of injections, the perceived risk of exposure to *B. anthracis* spores, and beliefs about the level of protection afforded by immunization against anthrax.

The CDC has developed a research agenda including projects designed to study adverse events and correlates of immune protection and to increase the acceptability of the anthrax vaccine. At the same time, other projects will address the administration of the vaccine so as to assure that changing the route of administration and the number of doses (so as to reduce adverse events) at least maintains the level of safety and efficacy of the current vaccine. The safety component focuses on true adverse events associated with immunization, including both improved accuracy in detecting adverse events and modifications to the product and its use that would reduce the likelihood of adverse events. The CDC research plan also includes projects addressing the acceptability of the anthrax vaccine.

The CDC has not yet described a comprehensive plan explaining how the projects fit its overall goals. The committee was not able to assess the plan's completeness and appropriateness with respect to its goals while the plan itself was still developing. At the time of this interim

report, it is not clear whether the CDC as a whole is approaching the research primarily with a view to changing the labeling of the current AVA product, or with a view to furthering scientific understanding of the anthrax vaccine and its use and context more generally. These goals are not inconsistent, but if both exist then a comprehensive plan should describe their integration. In any case, some of the studies planned by the CDC are not relevant to changing the labeling, but would be contributions to the wider context of anthrax vaccine research. It is therefore very important for the committee to understand as soon as possible how the CDC interprets that context, how they have identified missing elements which their plans will address, and what may yet remain to be done. In the absence of such a comprehensive plan, it is difficult for the committee to evaluate fairly the CDC's plans for completeness and appropriateness.

At the time of this interim report, the committee's general recommendations below reflect, first, the need for a comprehensive research plan from the CDC, that is, all the anthrax vaccine related research the CDC contemplates, and how that research would fit into the wider anthrax vaccine research context. In addition, the committee notes that the CDC often seems to be seeking scientific advice on specific points of protocol development of a highly technical nature that would be most useful to them if provided directly and immediately rather than in a formal published report. Finally, the committee notes the scientific importance, and also the scientific opportunity, attendant upon potential collaboration between the CDC and both the DoD and the NIH and encourages the CDC explore fully areas of such potential. The committee highlighted the example of analyzing potentially complementary databases, but also realizes other areas of collaboration may emerge in later discussion. The committee made general recommendations on these points (see [Box 2-1](#)).

#### **BOX 2-1 GENERAL RECOMMENDATIONS FOR CDC'S ANTHRAX VACCINE RESEARCH PROGRAM**

##### **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 the DoD wherever possible, including for example much more extensive use of DoD databases such as the Defense Medical Surveillance System (DMSS).

The NCID plans include a human clinical trial of changing the route of inoculation with the vaccine from subcutaneous to intramuscular, and reducing the total number of doses. Other NCID projects support and extend this work using animal trials and laboratory assays on basic pathogenesis, immunology, and correlates of immunity. The clinical trial and some elements of the laboratory and animal studies are directly and forthrightly designed to satisfy regulatory requirements of scientific support for a change in the labeling of the licensed anthrax vaccine AVA. The plans for the clinical trial and related studies seem to be complete and appropriate with respect to the goal of changing the labeling directions regarding route of administration and dosage schedule. Other related studies appear not to be necessary for the labeling change, but perhaps are important in the wider context of anthrax vaccine research. If so, then an assessment of the completeness and appropriateness of those other studies should properly be made from a different perspective, that of the larger research context. The apparently dual goal of the set of studies, in part to support a labeling change and in part for a wider research contribution, creates challenges for an overall review of the study plans. In particular, the committee noted several omissions in the set of study plans where the omitted study might be unnecessary for the labeling change but quite important in the wider research context, including future studies of safety and efficacy of products yet to be approved.

The primary elements of the CDC research plan under the purview of the NIP include studies of the knowledge, attitudes, and beliefs of populations regarding aspects of the anthrax vaccine immunization program (AVIP), and also include several approaches to making better and more intensive use of existing data relevant to the safety and the efficacy of the vaccine. These projects are clearly intended to contribute to the larger anthrax vaccine research context. In general, the NIP-sponsored studies are not as far along in their development as are the NCID-sponsored studies related to the labeling change. This interim report reflects two results of the difference in the development time lines. First, the studies that appear to be designed specifically with a view to supporting a labeling change get greater scrutiny at this time than do any of the studies pertaining to the wider context of anthrax vaccine research, simply because the committee received more detailed information for review and discussion. Second, the distribution of studies within the CDC results in the NCID-sponsored studies (since they are concerned with the labeling change) getting more scrutiny than the NIP-sponsored studies. Again, this is an artifact of the relative stage of development, and hence of the relative amounts of information available, in each case. The projects in either part of the CDC that were described in full or in part to the committee by the time of writing the interim report are listed in [Box 2-2](#).

### NCID RESEARCH ACTIVITIES

The NCID issued a call for proposals to carry out one or more parts of the following three-part research plan.

- Part A: Anthrax Vaccine Adsorbed (AVA): A Human Reactogenicity and Immunogenicity Trial to Address Change in Route of Administration and Dose Reduction
- Part B: Non-human Primate AVA Dose-Ranging, Immunogenicity and Challenge Trial
- Part C: Anthrax Pathogenesis, Immunology, and Correlates of Protection Against Inhalational Anthrax

### Part A: Clinical Trial

The Part A clinical trial is designed to evaluate the effects of changing the administration of the vaccine from the current subcutaneous (SQ) route to the more common intramuscular (IM) route, and to evaluate whether this change affects the rate of adverse events in male and in female recipients. Part A also will evaluate the efficacy of the vaccine under the new conditions, based on correlates of immunity, that is, laboratory tests of the level of antibody in the blood that is correlated with immunized humans and with animals that have been shown to be protected from infection. Then that information will be the baseline for evaluating the effects of reducing the total number of vaccine doses. The labeling currently specifies six doses given over 18 months, followed by annual boosters, but the study as currently planned will assess reducing that to as few as four doses over 18 months with boosters every two years. The trial will be double blinded, randomized, and controlled using saline as the placebo. The active treatments will use the current supply for the first four doses (lot FAV-048b), and a different lot (to be produced by BioPort, but used only if certified by FDA as releasable) for subsequent doses. Given the length of the data collection period, the trial must last at least three and a half to four years. [Box 2–3](#) summarizes the study design.

#### BOX 2–2 PROJECTS PRESENTED TO DATE IN CDC RESEARCH PROGRAM

##### NCID—in development

Part A: Anthrax Vaccine Adsorbed (AVA): A human reactogenicity and immunogenicity trial to address change in route of administration and dose reduction  
Part B: Non-human primate AVA dose-ranging, immunogenicity and challenge trial  
Part C: Anthrax pathogenesis, immunology, and correlates of protection against inhalational anthrax  
Human leukocyte antigen sub-study

##### NIP—in development or planned for development

Survey of knowledge, attitudes and beliefs (KAB) prevalent among military service personnel and also of military health care providers regarding the anthrax vaccine  
Survey of the KAB prevalent among military health care providers regarding practices of reporting to Vaccine Adverse Event Reporting System (VAERS)  
Data-mining in the VAERS database  
SF-36 Survey of clinical trial participants  
Hormonal correlates of adverse events in female clinical trial participants  
Long-term follow-up of any available previously immunized populations  
Meta-analysis of safety and efficacy studies on the anthrax vaccine

### BOX 2–3 STUDY DESIGN FOR PART A CLINICAL TRIAL

Purpose: To evaluate the effects of changing the route of administration from subcutaneous (SQ) to intramuscular (IM), and of reducing the number of doses.

Group	Route	Vaccine	N	Primary (wks)	Boost (mns)
1	6SQ	AVA	260	0–2–4	6–12–18–30–42
2	5IM	AVA/S*	260	0-S-4	6–12–18–30–42
3	4IM	AVA/S	260	0-S-4	6-S-18–30–42
4	4IM	AVA/S	260	0-S-4	6-S-18-S-42
5	IM	S	260	S-S-S	S-S-S-S-S

\*S=saline placebo

The research sites that will be participating in the Part A trial include Baylor College of Medicine in Houston, Texas; Emory University Vaccine Center in Atlanta, Georgia; The Mayo Clinic and Foundation in Rochester, Minnesota; and the Walter Reed Army Institute of Research in Silver Spring, Maryland. As shown above, the plans call for a total enrollment of 1300 participants; a new call for proposals has been issued in order to include an additional site so as to increase enrollment and meet that goal.

The committee found that the proposed research on changing the route of administration of the vaccine and reducing the number of doses required is appropriate. These results also are necessary from a regulatory perspective in order to change the vaccine product labeling so that the military could change its practice and remain in accord with FDA-approved guidelines.

The committee considers some potential modifications, particularly to one group, of the human clinical trial as perhaps advantageous, while recognizing that it may be difficult to implement any further changes at this date.

- **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 believes this could be done by modifying the regimen of the existing study group two, since that regimen has already been investigated in a pilot study. In the table in [Box 2–3](#) above, Group 2 would then appear as follows:

2 3IM AVA/S\* 260 0-S-4 6-S-S-S-S

The committee has not yet seen the methods section of the human clinical trial protocol, notably the specific types of statistical analyses that will be employed in the analysis of clinical trial data. The committee is concerned about the methods to be used.

- **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 recognizes that the human clinical trials are intended to investigate gender differences related to adverse reactions, as specifically mentioned in the Congressional mandate.

Previous work (Pittman et al., submitted for publication) has shown a significantly greater number and extent of local adverse reactions to subcutaneously administered anthrax vaccine in women. The CDC'S plans for recruitment of volunteers anticipates a sufficient number of female subjects, 20 percent of total enrollment, to detect a difference of similar degree, but not for a smaller difference. The CDC also plans a substudy of hormonal status that would further subdivide the female volunteers, so that study would require a larger number of participants. As planned, the clinical trial would be powered adequately to detect a substantial difference related to sex (a biological parameter) or gender (a psychological and/or social phenomenon) in the rate of adverse reactions to subcutaneous inoculation, given successful recruitment of female subjects. However, several factors may complicate such recruitment. Belief among potential recipients that women may suffer more reactions (also indicated in the Pittman study), and plans for recruiting study volunteers from, among other groups, first responders (traditionally professions employing more men than women), together cause the committee to doubt the likelihood of enrolling female volunteers in sufficient numbers to provide adequate power for the planned studies. As planned, this study will not have adequate power to address aspects of sex or gender differences beyond route of administration. The military population and organization, however, may provide especially good opportunities for additional research including pharmacoepidemiologic studies (Tilson, 1992; Strom 2000) or perhaps active surveillance among military personnel.

- **The committee recommends that the CDC consider, in addition to the proposed clinical trial, a prospectively designed pharmacoepidemiologic study of military vaccine recipients with both active surveillance and historical data from DMSS for moderate to 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 deliberated long and carefully regarding the use of saline, as opposed to the adjuvant aluminum hydroxide or alhydrogel. The question of which substance is the appropriate placebo reflects the question of what is the most important variable to measure in this trial, and thus to which vaccine component the participants and investigators must be blinded. Since the AVA product is the vaccine adjuvanted with aluminum hydroxide, the question of adverse events due to the product (the complete adjuvanted product) would be best addressed by an aluminum-free placebo such as saline solution. Alternatively, since the active ingredient is PA, the question of adverse events due to the antigen alone would best be addressed by an aluminum hydroxide placebo. The committee also discussed whether it would be ethical to use an aluminum hydroxide placebo. Some members argued that such a placebo would cause discomfort to the subject perhaps without any personal benefit, and others pointed out that the subjects would be civilian volunteers, not deployable and not likely to be exposed to biological weapons, and thus the groups receiving the vaccine would probably not benefit personally either. In the end, the committee did not develop a consensus on the best choice of the placebo.

### **CDC proposal for use of the Short Form 36**

The CDC proposed to add to the human clinical trials a self-assessment using the Short Form 36 (SF-36). The SF-36 is a survey instrument developed in 1992 by the RAND Corporation for self-assessment of health status. This survey has been very well studied and extensively validated. The committee found that the rationale for including such a measure in the human clinical trial was appropriate. However, the SF-36 can be augmented by existing, validated items

to address populations more specifically. Further, the time of administration of the survey is quite important so clinical personnel should have specific instructions about administering the survey, and also about the use of the results (as some may be relevant to the examination of the patient in the context of the immediate visit).

- **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.**

### **Part B: Non-human Primate Dose-Ranging and Challenge Study**

The animal studies would compare different doses of vaccine to establish the appropriate dose for the rhesus macaque, the animal species of interest, and the effect of reducing the number of doses on the animals' circulating antibody and ability to survive challenge with aerosolized anthrax.

The committee found that supporting animal studies are of great importance in an anthrax vaccine safety and efficacy research program. It is not possible to do a human clinical trial of vaccine efficacy for inhalational anthrax: the disease has a high fatality rate, and improved working conditions in goat hair and woolen mills, as well as increased use of synthetic materials, have (fortunately) eliminated the major source of naturally occurring cases in the United States. In brief, the strategy for supporting the efficacy of a vaccine for which human clinical trials with challenges could not be done is based on correlations of laboratory measurements in humans and animals. Some of these steps in anthrax vaccine may have been done or be underway but, in general, such a strategy might work like this:

- (1) Passive animal-animal immune transfer study: Immunize animals of a suitable species, measure levels of antibody, in serum, then give different concentrations of animal antibody-containing serum to naive animals (i.e., passively immunize the new animals). Then challenge the passively immunized animals along with some non-immunized control animals with aerosolized *B. anthracis* spores. Note the concentrations of antibodies associated with surviving the challenge.
- (2) Passive animal-human immune transfer study: Repeat using human antibody-containing serum from humans vaccinated with a full course of anthrax vaccine, then challenge the immunized animals (and controls). Note the concentrations of antibodies associated with surviving the challenge, and compare the levels of animal and human antibody needed to provide passive protection allowing animals to survive challenge.

The results provide a surrogate for clinical effectiveness of the vaccine, since clinical effectiveness in humans cannot be tested. The surrogate would be the ability of a vaccine to stimulate, in humans, levels of antibody correlated with the level necessary to protect animals from inhalational challenge by passive immune transfer.

Not all of this may be necessary for a labeling change in the current product, because as described in the previous chapter, the current product was developed using data from an actual human field trial (though of a slightly different vaccine and concentrating on cutaneous anthrax). But for development of future anthrax vaccine products, it will be absolutely necessary to establish a complete set of steps correlating animal immune response to circulating antibody in the fully immunized human. But because it was not entirely clear to the committee whether the



goal of some of the studies planned by the CDC was the labeling change only, or also the larger research context, it was likewise not entirely clear whether the research program was simply limited in scope, or seriously incomplete, in the absence of some steps in establishing the correlation sketched above.

As a model for effects in humans, animals that develop inhalational anthrax, rhesus macaques, will be immunized using different schedules. In earlier trials, however, the macaques received the same dose of vaccine as a human would, that is, much more vaccine per unit body weight than a human would receive. The CDC plans a dose-ranging study to establish the appropriate dose of vaccine for a rhesus macaque as a basis for future studies. The animals will be immunized with different dilutions of vaccine, and then their immune systems will be challenged by exposing them to a dose of aerosolized *B. anthracis* spores, to evaluate whether they will have developed an antibody level that protects them from infection. This study is being overseen by the Batelle Memorial Institute.

Often such a series of studies would be preceded by passive human-to-animal and animal-to-animal transfer studies as described above. The CDC's plans do not currently include such studies to demonstrate passive transfer of serum antibody to macaques and determine the level of antibody necessary for protection, and the committee believes this omission should be addressed either in the CDC plans, or by reference to work done or underway elsewhere, from the point of view of establishing correlation of immunity in the larger context of anthrax vaccine research.

The committee discussed the dose ranging trial at some length, with particular concern for the dilution series specified. The plan calls for two-fold dilutions *after* the first step of the series, which would be a 1:5 dilution, has large steps (1, 1:5, 1:10, 1:20, etc.). The committee suggested that the series might miss important information, and that the series should be two-fold all along (1, 1:2, 1:4, 1:8, etc.). The committee emphasized further that the basis of these (and many future) studies should be a passive antibody transfer study, as previously discussed. The committee concluded finally that the CDC research plan remained incomplete in that it lacks a study demonstrating passive transfer of human serum antibody to macaques and determining the level of antibody necessary for protection, unless such a study is known to be underway elsewhere.

- **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 appropriate dilution series.**

The design of the challenge study is shown in [Box 2–4](#) below. The committee did not make additional recommendations on the challenge study, but urges, as in the case of the human clinical trial, careful consideration at the outset of appropriate methods of statistical analysis.

### **Part C: Assays of Immunologic Correlates of Protection**

Part C is related to both Parts A and B above. Part C is a series of assays, listed in [Box 2–5](#) below. The overall goal of the series is to validate currently proposed immunologic correlates for protection, especially anti-PA antibody levels, and possibly to identify new immunologic or genetic correlates of protection.

The Part C Assays are to be carried out by Emory University and overseen by the Batelle Memorial Institute, which has arranged subcontracts with Ohio State University in Columbus, Ohio, and with the Centre for Applied Microbiology and Research in Porton Down, United Kingdom.

### BOX 2-4 STUDY DESIGN FOR PART B NON-HUMAN PRIMATE TRIAL

Purpose: To evaluate the effects of dropping doses at 12 and 30 months on immunogenicity and survivability, to determine the amount of circulating antibody at challenge, and to assess the role of memory response.

Group	Route	N*	Schedule	Aerosol Challenge
1	IM	10	0-4 wks, 6 mns	12 mns
2	IM	10	0-4 wks, 6 mns	18 mns
3	IM	10	0-4 wks, 6-18 mns	30 mns
4	IM	10	0-4 wks, 6 mns	30 mns

\*+2 controls for each group

### BOX 2-5 PART C ASSAYS

- T Cell proliferation, activation, cytokine production
- Enumeration of PA, LF, and EF specific plasma cells
- Cytotoxic T cell responses to anthrax toxin
- Anti-PA monoclonal antibodies for epitope mapping of the PA toxin
- Anti-PA, EF, LF ELISA
- Anti-PA IgG subclasses 1-4 ELISA
- TNA titers as measured by PA-633-LF cytotoxicity, LF endopeptidase inhibition, EF adenylate cyclase inhibition assays
- Opsonophagocytosis via flow cytometry using HL-60
- mRNA and protein levels of TH1 and TH2 cytokines
- cAMP assay
- High-avidity serum IgG ELISA

The Part C assays use blood drawn from the Part B non-human primate trials and also from the Part A human trials. The committee found that the scientific account of immune correlates has developed rapidly and commendably in the case of the plans for most of the assays. One assay proposed by the CDC, however, was still not fully explained. The CDC proposes to use microarray technology to assess whole-cell gene expression in response to vaccination or challenge. The CDC noted at the time of presentation that the technical proposal for use of this assay was still in development; indeed, at that time the rationale for the use of microarrays was not yet clear to the committee. The committee was also not convinced, however, that the Opsonophagocytosis assay as described would be likely to be very informative.

- **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 CDC also plans two substudies in association with the Human Clinical Trial or Part A. These two studies seem not to be intended to support a labeling change, but rather to contribute to the wider research context. Again, the problem is that it was not clear to the committee at this stage in the development of the overall research program how the CDC envisions these particular studies fitting into that wider context. One of these would be to investigate at one study site, the

Mayo Clinic, any influence of human leukocyte antigen (HLA) on immune response to the anthrax vaccine. The committee found that the rationale for the HLA substudy was not yet complete and recommends further explanation of its role if it is to be part of the CDC's research program. The other substudy would address whether there is any association between progesterone levels and vaccine adverse events among women. The committee found that it had not yet heard the plans in sufficient detail to make a full assessment of the study. The committee did express doubt about the likelihood of recruiting sufficient female volunteers to carry out the investigation with adequate power, as was discussed under Part A above.

### NIP RESEARCH ACTIVITIES

The NIP has begun work on a variety of types of research, including studies of the personnel actually involved in the vaccination program, either as intended recipients or as health care providers, and also studies to make further use of existing data. As previously mentioned, these studies appear to be intended as contributions to the wider context of anthrax vaccine research, not to the particular immediate project of changing the labeling. The NIP has proposed studies that are quite varied in technique and rationale, and at the time of writing the interim report, also varied widely in degree of development. The committee kept in mind the preliminary nature of the proposals while assessing the program. On the basis of the information presented to date, the committee looks forward to further review of comprehensive, and of additional detailed, information as soon as it is available.

#### **Knowledge, Attitudes, and Beliefs of Military Personnel about the Anthrax Vaccine**

The NIP has requested proposals to carry out a survey of the knowledge, attitudes, and beliefs (KAB) prevalent among military personnel regarding the anthrax vaccine. This study, which has not yet begun, will be designed to describe the KAB of military service personnel in general and also of military health care providers regarding immunization against anthrax. The resulting descriptive information will, it is hoped, provide the basis to assess the reasons for concern about anthrax vaccination and the educational needs pertaining to the anthrax vaccinations of the populations studied.

The first step of the study would be to gather information from a series of focus groups, in order to develop a survey instrument informed by a broad and representative example of individuals from the study population. The actual survey was planned to include a sample of some 14,000 individuals using cluster sampling to assure representation of all service and regional components of the military population. In all cases, participants would be asked to complete the survey in a classroom setting (and rewarded with a non-monetary incentive), in order to avoid the consistently low rate of returns from mailed surveys. After the first survey and a sufficient period for planned interventions (expected to be two to three years), a follow-up survey would be administered to a newly selected group (again, selected by cluster sampling, and preceded by a focus group exercise). Finally, in order to evaluate more reliably the effectiveness of the interventions in affecting the KAB of services personnel, the overall study design incorporates a longitudinal subgroup—a small cohort that will be identified in the first large survey and then relocated and resurveyed in the second part of the study (see [Figure 2–1](#)).

The committee found that the rationale for investigating the KAB of service personnel was appropriate. The committee found, however, that the plans for the study were incomplete with respect to plans for the design of the educational interventions and survey instrument, and

commented that entire study might be strengthened by investing more in its design phase. For example, in addition to careful use of focus groups, the educational interventions could be refined through cognitive tests in small groups so that both the educational interventions and the survey instrument were more sharply focused in purpose and therefore more effective. The committee also would appreciate further discussion of how the protocol design will address the turnover in the military between surveys. The committee anticipates that plans for this study could undergo significant further development, and will be very interested in any further information.

In public hearings the committee heard from current and former military service members outside the health care system about their perceptions of the military health care system. The KABs of both patients and providers are crucial in any health care program; in the anthrax vaccine program in particular, the need to understand the KAB of all involved parties is pressing. The committee heard expressions of significant concern from current and former military service personnel, supporting the importance of obtaining reliable KAB information. The committee also found that the KAB of health care providers would be likely to differ from military personnel in general and to play an especially important role in forming perspectives on the use of the anthrax vaccine, indicating possible need for a different survey instrument in the case of this group. Such a survey might be carried out in combination with another planned survey of military vaccine providers, discussed further below. Additionally, both surveys—or perhaps even a third, specifically directed survey—might profitably be designed to generate important information about perceptions of the military health care system. Concerns about the AVIP, and the use of civilian as well as military health care facilities, may have effects on the KAB of military personnel, as the military may be perceived by some service personnel (however unfairly) as taking a less direct interest in the health of its troops. That perception might then affect the confidence and trust of military patients in their health care providers and the military health care system. Finally, the committee found that there was currently insufficient justification for the sample size suggested.

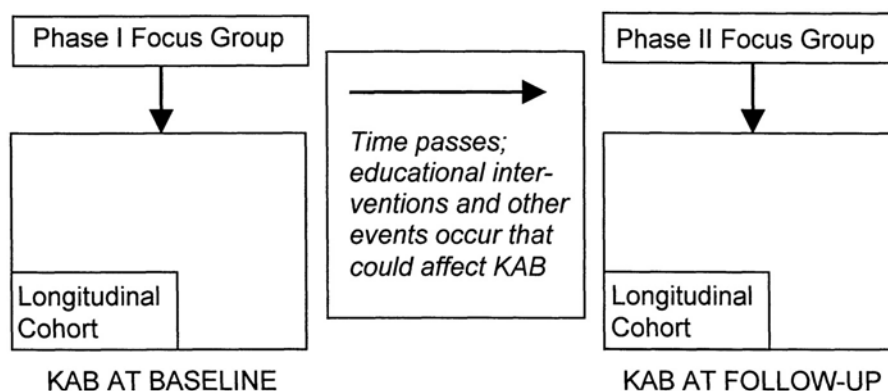


Figure 2-1 KAB Survey of Military Personnel Regarding the Anthrax Vaccine

- 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.

### Knowledge, Attitudes, and Beliefs of Vaccine Providers about VAERS Reporting

The NIP has requested proposals to carry out another type of survey of the KAB prevalent among military and civilian providers of military vaccines regarding reporting to the Vaccine Adverse Event Reporting System (VAERS). This study, which shares some elements of its design with the study described just above, also is not yet underway. In this case, the descriptive information gathered in the study should allow the assessment of the level of awareness and knowledge of VAERS among vaccine providers, factors affecting reporting of adverse events among vaccine providers, and providers' beliefs regarding both the ease and the utility of reporting adverse events. Again, the study is planned as two surveys. These surveys will be conducted by telephone interview to avoid the low return rate of mailed surveys. The populations surveyed will include military physicians and nurses; other military health care providers, especially vaccine providers; civilian physicians and nurses; and public health clinic staff members, again using cluster sampling to assure diversity in the sample.

The committee heard testimony from some concerned service members and other citizens indicating that they believe that the anthrax vaccine may be associated with more adverse events than reflected in VAERS, due at least in part to aspects of military life that may tend to discourage the reporting of adverse events. Based on the information available at the time of this report, the KAB study of health care providers with respect to VAERS reporting seems to be directed primarily toward investigating that concern, that is, toward *enhancing* VAERS reporting, especially in the military.

The committee also observed, however, that as a passive surveillance system, VAERS can never be expected to serve as a source of information about the true rate of adverse events. Specifically, the rate of reporting adverse events is typically low relative to the true rate of adverse events, and fluctuates for many reasons. In the particular case of the anthrax vaccine, it may be that military culture has in some way tended to discourage reporting, but at the same time it may also be that publicity from news coverage and congressional hearings has tended to encourage reporting. In order to use information from VAERS regarding the anthrax vaccine, it would therefore be very important to compare reporting related to the anthrax vaccine, to reporting related to other vaccines such as tetanus and influenza.

Incidence rates cannot be determined from spontaneous reports, so low numbers of VAERS reports about a product cannot definitively establish the safety of the product. Such low numbers reflect an absence of a signal of a problem and can never substitute for data from a formal pharmacoepidemiology study evaluating safety. Low numbers are thus consistent with (but not proof of) safety, and high numbers might likewise signal the lack of safety (but cannot definitively establish that either), as generally nothing definitively causal can be concluded from a passive surveillance system (Tilson, 1992).

There is a further difficulty indirectly implied in the plans for this study. The study includes surveys at two time points. It is the committee's impression from this and other aspects of the CDC's program that the CDC expects to undertake educational and other activities in the hope of increasing VAERS reporting, presumably by changing the KAB of health care providers who do most of the reporting.

The committee certainly has no objection to education about VAERS, nor to increasing the reporting rate for this or any other product. But if there were to be a change in the absolute number of VAERS reports following such educational and other activities, both the change and the number would be uninterpretable in the absence of some reference standard for the rate of

adverse events themselves. Without some independent measure of the rate of adverse events, it would be impossible to decide whether a change in the number of adverse event reports occurred as a result of a change in the number of adverse events, or a change in the KAB of health care providers regarding reporting. That would be a serious problem, because the value of VAERS is as a signaling system: a sudden increase in adverse event reports associated with a particular vaccine may indicate a problem with a particular lot of the product, for instance, and thus serves to alert both regulators and industry to investigate. To the extent that such a change might reflect changed attitudes about reporting rather than a change in the product administered, VAERS could no longer serve its signaling function.

The centralized military health care system may offer ways to devise a solution. For example, the committee also received information regarding the Defense Medical Surveillance System (DMSS), which receives records of medical encounters on both inpatient and outpatient visits for all service members. The DMSS database may thus provide an independent source of information on vaccinations and medical encounters and complaints following vaccinations.

The committee found that the rationale for investigating the KAB of health care providers toward VAERS was appropriate, but cautioned that since this activity and associated educational interventions could affect VAERS reporting, it should be associated with an independent source of information about adverse events. The committee commented that data from the DMSS, which tracks the medical encounters and other pertinent data on military personnel, offers such an independent comparison at least for moderate and severe adverse events, and noted further that this is an example of an area of potential collaboration between the CDC and the DoD. Furthermore, the committee found that the survey of military vaccine providers regarding VAERS might be coupled with the segment of the survey regarding the stance of health care providers toward the anthrax vaccine, as mentioned above. Finally, the committee found that previous research on VAERS reporting would justify reconsideration of the sample size, perhaps reducing the number of subjects.

- **The committee recommends that the CDC consider expanding the design phase of the knowledge, attitudes, and beliefs (KAB) study of military vaccine providers regarding the Vaccine Adverse Event Reporting System (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 knowledge, attitudes, and beliefs (KAB) of health care providers regarding the anthrax vaccine in the study now designed to assess only KAB on the Vaccine Adverse Event Reporting System (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 Defense Medical Surveillance System (DMSS), when assessing any monitoring of, or modification to, Vaccine Adverse Event Reporting System (VAERS) reporting practices and VAERS analyses.**

#### Data Mining Using the VAERS Database

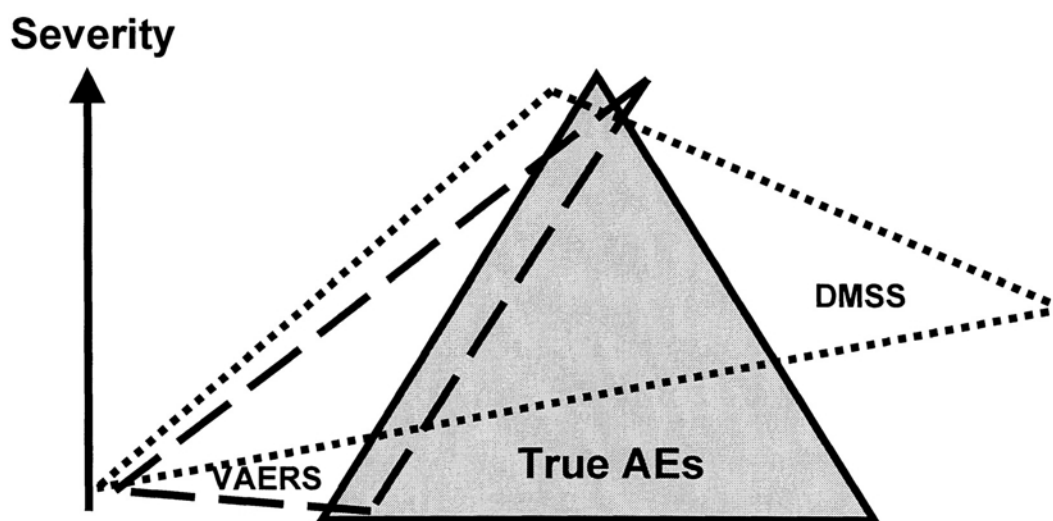
Despite the limitations inherent in a passive surveillance system, the VAERS database is a rich lode of information, and the CDC has designed a data-mining study to exploit that resource.

Although passively accumulated, the data may well yield information from systematic clusters of symptoms that could be identified through careful and structured analysis of the data available. The CDC has reviewed several software packages especially designed for seeking patterns in the data, and was pleased to find the SAS Cluster package, a familiar tool, among the top contenders. Another approach to local structure representation is the detection of self-organizing maps (this effort is not being funded as part of the CDC's anthrax vaccine research, but the results may nevertheless be relevant). As well as local structure, the database may exhibit some global patterns, which could be a basis for building statistical models of the factors involved. Various methods for global structure representation exist. The CDC is working mostly with empirical Bayes models. Finally, the CDC is pursuing several hybrid approaches such as using factor analysis and logistic regression to attempt to reduce the number of variables that could possibly be relevant through the identification of structure underlying adverse events, then developing a logistic model to predict from those factors which vaccine had been given.

Since VAERS is a passive surveillance system, as has been discussed previously, it is virtually guaranteed to include reports that are duplicative, incomplete, or inaccurate, in addition to the fact that the rate of reporting typically will be low. As a result, data-mining techniques must be employed with care, and even more, any results should be reported so as to reflect the uncertainties implied by the data themselves. That is, the committee is concerned that the evaluation of data mining techniques applied to VAERS data is challenging, and encourages the CDC to explore thoroughly the use of complementary data bases such as DMSS in this context. For example, while VAERS is most useful for detecting trends emerging over time, the data-mining techniques described to date do not have a time dimension. The committee has not yet heard enough about this project, which is still in a very early phase of development, to make many specific recommendations about the CDC's plans. It is important to consider complementary analyses of the VAERS and DMSS databases because of the different characteristics of the two systems. The VAERS is an entirely voluntary system that receives any reports that are submitted depending on the level of interest and concern on the part of the vaccine recipient, the parent, or the health care provider. Its main value lies in its signal-capturing capacity: either by recording unusual events from large numbers of vaccine recipients during the post-marketing phase or by noting obvious changes in the trend of adverse event (AE) incidence that might suggest problems with the vaccine product or particular lot. DMSS is a database that collects records of all medical encounters in the military health care system, as well as anthrax vaccinations. It would therefore include data on visits that would be within some given time after an anthrax vaccination, and the ICD-9 code of those visits. For the purpose contemplated here, one of the main values of DMSS is its relative completeness with respect to medical encounters. Another reason the two systems may be complementary is that their different characteristics mean that the reports that are in each database reflect a different set of factors influencing what is to be reported.

Certainly there are adverse events of varying severity and frequency that are caused by vaccines in some cases. Also there are surely symptoms suffered by individuals who have recently been vaccinated but which are in fact caused by something other than the vaccine. Decisions either to report to VAERS or to seek medical advice can be influenced by many factors. So *both* the VAERS and the DMSS systems would be expected to capture some, but not all, of the true vaccine-caused adverse events, and both would also be expected to capture some, but not all, symptoms following vaccination that were actually caused by something other than the vaccination. But each would likely capture a different subset, or a subset influenced by

different factors. And both would be expected to capture a greater percentage of the serious AEs than the percentage they capture of the milder AEs. Figure 2–2 represents these relationships; please note, however, that Figure 2–2 is not drawn to any scale; it depicts only logical, not quantitative, relations.



**FIGURE 2–2** Schematic (not quantitative) illustration of potential relationships between the set of adverse events actually caused by the product itself (labeled “true”), and the subsets captured by DMSS and by VAERS. Unshaded space enclosed in the DMSS and VAERS segments represents symptoms that occur following vaccination, but were caused by something other than the vaccination.

### Meta-Analysis of Existing Studies on the Anthrax Vaccine

Since the data and information pertaining to the anthrax vaccine come from different types of studies over the decades, the CDC also intends to carry out a meta-analysis of a wide selection of safety and efficacy studies. The term “meta-analysis” here means a two-stage process of first developing and carrying out a structured search and systematic review of the available literature, followed by a combination, also structured and systematic, of the findings to produce a single overall estimate of the safety and the efficacy of the vaccine. The search for literature will begin with the safety review of the anthrax vaccine carried out by the DoD’s AVIP, and additional Medline searches and consultation of references and specialists. After the first step (the structured collection, review, and scoring of each paper), then the data from each paper must be extracted and converted to some common scale in order to permit combination of all data to obtain overall estimates. As neither populations nor study methods may be homogeneous, this step of the meta-analysis involves a number of assumptions, which must be made explicit.

The first step of a meta-analysis, namely, a systematic review of the literature, can certainly be undertaken and, if it has not already been done, certainly should be pursued as soon as possible. The next step, however, not only requires multiple assumptions as noted but, in order to be at all useful, requires many studies to be reviewed for combination. Prior to carrying out the combining of results, it will be important to determine whether the literature even contains enough studies of the safety and efficacy of the anthrax vaccine to make combination necessary or worthwhile, as well as reliable. The committee has not yet heard enough about this project,



which is still in a very early phase of development, to make any specific recommendations but will await the assessment of the number of studies, and then further discussion of how or whether to proceed with a meta-analytic combination.

In conclusion, the committee recognized great progress in the development of specific scientific studies over the course of the IOM committee's review to date. The committee looks forward to receiving further information and protocols as the CDC continues to develop its overall anthrax vaccine safety and efficacy research program.

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## ACRONYMS

ACIP	Advisory Committee on Immunization Practices
AVA	Anthrax Vaccine Adsorbed
AVEC	Anthrax Vaccine Expert Committee
AVIP	Anthrax Vaccine Immunization Project, DoD
CDC	Centers for Disease Control and Prevention
DMSS	Defense Medical Surveillance System
DoD	Department of Defense
EF	Edema Factor
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food and Drug Administration
HLA	Human Leukocyte Antigen
IOM	Institute of Medicine
IM	Intramuscular
KAB	Knowledge, Attitudes, and Beliefs
LF	Lethal Factor
NCID	National Center for Infectious Diseases, CDC
NIH	National Institutes of Health
NIP	National Immunization Program, CDC
PA	Protective Antigen
SQ	Subcutaneous
TNA	Toxin Neutralizing Assay
USAMRIID	U.S. Army Medical Research Institute for Infectious Diseases
VAERS	Vaccine Adverse Events Reporting Surveillance

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## Appendix A

### Study Activities

As contracted with the sponsor, the Centers for Disease Control and Prevention (CDC), the Institute of Medicine convened a committee that was charged with reviewing the CDC's anthrax vaccine safety and efficacy research program. In particular, the committee was to address risk factors for adverse reactions, including gender differences, immunologic correlates of protection and the documentation of vaccine efficacy, and the optimization of 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 requested this interim report 10 months after the project was initiated. The entire project leading to production of a full report reviewing the CDC's anthrax vaccine research program was planned for 24 months, to be completed contingent upon funding for the second year.

The committee included members with expertise in infectious disease epidemiology; vaccinology; drug/vaccine research, development, testing, and evaluation; post-marketing surveillance of adverse events, including the Vaccine Adverse Events Reporting System (VAERS); regulatory and licensing procedures; gender differences in adverse events reporting; and health surveillance. The committee met on October 31, 2000; on February 8 and 9, 2001, and on April 18 and 19, 2001. The meeting of April 18, 2001 included a public hearing, held jointly with the related Committee to Assess the Safety and Efficacy of the Anthrax Vaccine (sponsored by the Department of Defense), so that interested members of the public could address the committees.

All open meetings were announced in the IOM's Current Project System, pursuant to the Federal Advisory Committee Act as amended in 1997, and all materials submitted to the committee were made available through the IOM's Public Access File.

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## Appendix B

### Biographical Sketches

**Philip Brachman, M.D.** (*Chair*), is currently 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 and biostatistics in Atlanta and overseas. Dr. Brachman's current research activities include public health surveillance and nosocomial infections. He also directs the Hubert H. Humphrey Fellowship program, 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.

**Trudy Bush, Ph.D., M.H.S.**, was Professor and Director of the Graduate Program in the Department of Epidemiology and Preventive Medicine at the University of Maryland School of Medicine through March 2001. She was a cardiovascular epidemiologist by training, and her work focused on two primary areas: the epidemiology of cardiovascular disease in women and in older people and the effects of exogenous hormones on disease risk in women.

**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. 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, 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, and Director of the Clinical Microbiology Laboratory at the University of Minnesota Medical School. Her research interests include protein antigens of Group B streptococci, pathogenesis of infection, and host immunity. In addition, she is involved in molecular epidemiology, neonatal infections, and bacterial vaccines. She is a 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 prevention of groups A and C meningococcal meningitis. His research has also been directed at surface structures responsible for pathogenicity of gonococci and group B streptococci. Dr. Gotschlich is a fellow of the American Academy of Microbiology and a member of both the National Academy of Sciences and the Institute of Medicine.

**Maurice Hilleman, Ph.D., D.Sc.**, serves as Director, Merck Institute, where he has spent 42 years. 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 vaccines for 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), as well as a member of both the National Academy of Sciences and the Institute of Medicine.

**Dennis 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 bacterial structures such as capsular polysaccharides, surface proteins, and toxins. The ultimate goal of this research is to develop vaccines to prevent bacterial infections, notably those with group B streptococci.

**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 Com

mittee 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 Chair and Professor of Biostatistics & Epidemiology, Professor of Medicine, Professor of Pharmacology, Director of the Center for Clinical Epidemiology & Biostatistics, and Chair of the Graduate Group in Epidemiology & Biostatistics, all at the University of Pennsylvania School of Medicine. His clinical 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 over 280 original papers as well as one of the first textbooks in the field. Dr. Strom has served as President of the International Society of Pharmacoepidemiology and as a member of the Board of Regents of the American College of Physicians, and 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 Health Care Organizations, and the Drug Utilization Review Advisory Committee on the United States Pharmacopoeia Convention. He was elected to the American Society for Clinical Investigation, the American Epidemiologic Society, and the Association of American Physicians.

**Hugh H. Tilson M.D., Dr.P.H.**, is Clinical Professor of Epidemiology and Health Policy and Senior Advisor 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 which spans more than 30 years and includes service as a director of both state and local health departments, and as Vice President for Worldwide Epidemiology, Surveillance, and Policy Research at Glaxo Wellcome. He is an author of over 100 papers in the field of epidemiology, outcomes and policy research, and public health; a fellow of the American College of Epidemiology; and a 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 regulatory and government agencies as well as pharmaceutical companies as an advisor and consultant in health outcomes, drug safety, and evidence-based health policy.