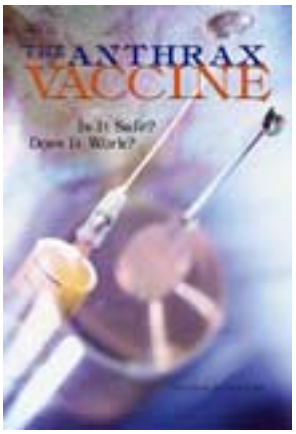
March 2002

INSTITUTE OF MEDICINE

Shaping the Future for Health

THE ANTHRAX VACCINE: IS IT SAFE? DOES IT WORK?



In autumn of 2001, anthrax and the anthrax vaccine became prominent national concerns. Deliberate distribution through the mail of spores of the bacteria that cause anthrax resulted in at least five deaths and 13 non-fatal infections, and thousands of people receiving treatment for known or suspected exposure to the spores. Along with the entire nation, public health and health care professionals found themselves facing many new questions about the disease, its treatment, and its prevention.

These events lent urgency to an Institute of Medicine (IOM) study already under way on the vaccine currently used to protect humans against anthrax, called Anthrax Vaccine Adsorbed (AVA). Licensed in 1970, AVA was used initially on a relatively limited basis, primarily to protect people who might be exposed to anthrax spores where they worked, such as veterinarians and textile plant workers who process animal hair. Use of AVA expanded in 1991, when the U.S. military, concerned that Iraq possessed biological weapons containing anthrax spores, administered the vaccine to an estimated 150,000 service members deployed for the Gulf War. With subsequent confirmation of an Iraqi bioweapons program, the Department of Defense (DoD) in 1997 announced a plan for the mandatory vaccination of all U.S. service members. To be phased in gradually, the Anthrax Vaccine Immunization Program began in March 1998 with personnel scheduled for deployment to high-risk areas, such as South Korea and Southwest Asia.

In addition to assessing how well AVA works and its safety, the committee would review and evaluate the process by which the vaccine manufacturer "validated," or fully documented, its production methods in order to gain FDA approval.

EMERGING CONCERNS PROMPT STUDY

As more service members were vaccinated, however, some of them raised concerns about the safety and efficacy of AVA, and some also suggested a possible link between AVA vaccination and the illnesses experienced by some Gulf War veterans. In addition, concerns emerged regarding manufacture of the vaccine. In early 1998, the sole facility for the production of AVA was closed for renovation. In 1999, BioPort—the Michigan company that now

owns the facility—resumed limited production of AVA, but the Food and Drug Administration (FDA) prohibited release of any new vaccine until the company demonstrated that its renovated production process met all federal regulations. BioPort received FDA approval in January 2002 and may begin shipping new vaccine supplies in March 2002. During the interval, however, vaccine supplies had dwindled, and by 2000 DoD had greatly slowed its vaccination program.

ANTHRAX: THE DISEASE

Anthrax, caused by the bacterium *Bacillus anthracis*, usually is confined to animals, such as cows and sheep. Historically, humans have contracted the disease through exposure to animals or animal products, such as hair or hides, that are contaminated with anthrax spores. The spores, which are dormant forms that the bacteria assume in response to hostile living conditions, are extremely hardy, can survive in the environment for generations, and can be spread readily through the air—traits that make them attractive for use in biological weapons or in terrorist attacks.

There are three basic forms of anthrax disease, depending on how infection takes place. Cutaneous anthrax may occur when spores penetrate the skin, usually through a cut or abrasion. Gastrointestinal anthrax may follow consumption of contaminated meat. Inhalational anthrax may result from breathing airborne spores deep into the lungs. Once in the body, through whatever route, the spores germinate into active bacteria that produce harmful toxins. Cutaneous infections are the most common, but usually respond to antimicrobial therapy. Inhalational infections have been relatively rare, but are often rapidly fatal, which is why this form of the disease generates particular concern in terms of potential terrorist attacks or biowarfare. None of the forms of anthrax is considered contagious, and person-to-person spread of the disease is highly unlikely.

In response to these concerns, Congress directed the Department of Defense to support an independent examination of AVA. In October 2000, the IOM established the Committee to Assess the Safety and Efficacy of the Anthrax Vaccine to carry out this study. In addition to assessing how well AVA works and its safety, the committee would review and evaluate the process by which the vaccine manufacturer "validated," or fully documented, its production methods in order to gain FDA approval. The committee also was asked to identify gaps in research regarding the anthrax vaccine.

The committee recognized that it was dealing with difficult issues: scientifically, it was dealing with a series of questions on which published data were limited, and politically it was operating in a charged arena, where strong positions had been taken and strong emotions expressed. Thus, the committee chose to be as open as possible, while maintaining maximum scientific rigor. It elected to hear from all groups and individuals who had anything to contribute, whether data, concerns, or complaints. Both published and unpublished data were sought, reviewed, and weighed in the committee's assessment. The committee's inquiries also triggered the development of significant new data related to the safety of AVA.

In March 2002, the committee issued its report: *The Anthrax Vaccine: Is It Safe? Does It Work?*

VACCINE EFFICACY

AVA is administered in a series of six subcutaneous (under the skin) injections. After the initial dose, shots are given at 2 weeks, 4 weeks, 6 months, 12 months, and 18 months. An annual dose of the vaccine is also given to boost immunity. AVA produces protection in the same way other vaccines do. Its primary active ingredient is a protein called protective antigen, which the anthrax bacteria release during the infection process. When injected as part of the vaccine, this antigen stimulates the body's immune system to produce antibodies that can recognize a future bacterial invasion and trigger a strong defense—thus, rendering the person immune to infection.

[The committee] elected to hear from all groups and individuals who had anything to contribute, whether data, concerns, or complaints.

Does AVA perform as expected? After examining evidence from several types of studies, in both humans and animals, the committee concluded that AVA, as licensed, is an effective vaccine to protect against anthrax, including inhalational anthrax. Moreover, because the vaccine exerts its protection via an antigen crucial to the action of the bacterium's toxins, AVA should be effective against anthrax toxicity from all known strains of anthrax bacteria, as well as against any strains that might be bioengineered by terrorists or others. The committee also noted that, based on limited animal studies, AVA administered in combination with antibiotics *following* exposure to anthrax spores may help prevent the development of inhalational anthrax.

While the fundamental issue of AVA's efficacy is settled, more remains to be learned. Because efficacy studies involving exposure to anthrax are neither feasible nor ethical in humans, animal studies are essential. One need is to establish a quantitative correlation between the levels of antibodies found in animals that are given AVA and develop protection against anthrax infection and the levels of antibodies found in humans after full immunization. Those correlates in animal models can then be used to test the efficacy of AVA, as well as new vaccines, with confidence that the animal data will be predictive of clinical results in immunized humans. Among the committee's research recommendations:

- ***Studies are needed to describe the relationship between immunity and both specific and functional quantitative antibody levels.*** This will include determining the relationship between the vaccine dose and the resulting level of antibody in the blood of test animals that protects them from bacterial challenge, the relationship between the level of antibody that protects animals and the level of antibody that occurs in humans vaccinated by the regimen currently recommended for AVA, and the vaccine dose that results in a level of antibody in the blood of human volunteers similar to that of the protected animals.

- ***DoD should pursue or support additional studies on the efficacy of AVA in combination with antibiotics administered following inhalational exposure to anthrax spores.*** One goal should be to establish how long antibiotics should be administered after vaccination to provide protection.

VACCINE SAFETY

Vaccines are critically important tools for preventing serious infectious diseases such as anthrax. As with any pharmaceutical product or medical procedure, however, use of a vaccine carries a risk of adverse health effects, which must be weighed against the expected health benefit. Safety expectations for vaccines are especially high because they are usually given to healthy people to protect them against a disease to which, ultimately, they may never be exposed.

After examining data from numerous epidemiologic studies, as well as from case reports, the committee concluded that AVA is acceptably safe.

After examining data from numerous epidemiologic studies, as well as from case reports, the committee concluded that AVA is acceptably safe. It is fairly common for people to experience local reactions (such as redness and swelling at the injection site), and for a smaller number to experience systemic reactions (such as fever and malaise), within hours or days of vaccination. But such reactions soon go away on their own. Also, these reactions, and the rates at which they occur, are comparable to those observed with other adult vaccines. The committee found no evidence that people face any increased risk of experiencing life-threatening or permanently disabling adverse events immediately after receiving AVA, when compared with the general population. Nor did it find any convincing evidence that people face elevated risk of developing adverse health effects over the longer term, although data are limited in this regard (as they are for all vaccines).

Still, the committee concluded, efforts are needed both to improve how AVA is currently used and to expand monitoring efforts to detect any adverse health effects caused by AVA or other vaccines used by military personnel. Among the recommendations:

- ***DoD should continue to support the efforts of the Centers for Disease Control and Prevention to study alternative routes and schedules for AVA injections.*** The current subcutaneous route of injection and the six-dose schedule appear to cause a higher incidence of local reactions than is seen with a reduced-dose vaccination schedule or with intramuscular (into a muscle) administration, which is the route employed for most other vaccines.

- ***Future monitoring and study of health events following anthrax vaccination, as well as vaccination for other diseases, should continue to include separate analyses of data for men and women.*** Current data indicate that women experience local reactions from AVA and other vaccines more frequently than do men. The factors that account for these gender differences are not known, but may include differences in dose per unit of body mass, differences in physiology, or differences in care-seeking behavior.

- ***DoD should develop systems to enhance the capacity to monitor the occurrence of later-onset health conditions that might be associated with the receipt of any vaccine.*** The data do not suggest the need to develop special ef-

forts of this sort for AVA alone.

VACCINE MANUFACTURE

The committee could not directly evaluate the AVA production process used by its manufacturer, BioPort, and did not find it necessary to second-guess the FDA's inspection and ultimate validation. It was possible, however, to review and evaluate the steps taken by the company to gain approval of its AVA production process. The bottom line: with the newly validated manufacturing process being used in an updated and validated facility, AVA will be produced under strict controls according to current FDA requirements. This promises greater assurance of consistency in the newly produced vaccine than was the case for the vaccine produced at the time of its original licensure.

… with the newly validated manufacturing process being used in an updated and validated facility, AVA will be produced under strict controls according to current FDA requirements.

FUTURE NEEDS

Current events strongly suggest not only the possibility that the military will speed up its anthrax vaccination program, but also that the government will expand vaccination to newly recognized high-risk persons in the civilian population.

With this prospect of increased vaccine use, the committee concluded that heightened efforts are needed to improve the way AVA is now used, to expand and sharpen surveillance efforts to detect adverse health events related to its use, and to develop a better vaccine. Among the committee's recommendations:

- ***AVA produced in the renovated facility should be monitored for immunogenicity, stability, and possible acute or chronic adverse events of immediate or later onset.*** Such continued testing is required of all vaccines. Although greater product consistency seems likely given the newly validated manufacturing process, the actual levels of immunogenicity (whether it generates adequate levels of antibodies), stability (whether it remains consistently potent over time), and safety must nevertheless be characterized empirically.

- ***DoD should develop a capability for effectively using the Defense Medical Surveillance System (DMSS) to regularly test hypotheses that emerge from the Vaccine Adverse Event Reporting System (VAERS) and other sources regarding vaccine-related adverse events.*** VAERS is the nation's principle mechanism for collecting reports on adverse events following the use of any vaccine licensed in the United States. DMSS, a set of health-related databases administered by the Army, brings together information from each of the armed services. With data for service members' entire length of service, DMSS provides a longer period of observation than is available with most vaccine safety studies. To maximize the usefulness of this system, DoD should support and advance the development of DMSS data resources and the staffing of units necessary to foster rapid and careful continuing analyses of these data. DoD also should investigate mechanisms to make DMSS data

available to civilian researchers (with appropriate protections of privacy).

- ***DoD should evaluate options for longer-term follow-up of possible health effects of anthrax vaccination (and other service-related exposures).*** Among the specific steps to be considered are encouraging participation in the Millennium Cohort Study, which will follow 140,000 military personnel during and for up to 21 years after their active service to evaluate the health risks of military deployment; collaborating with the Department of Veterans Affairs to monitor service members who receive VA medical care after they leave the service; and ensuring maintenance of DMSS data and various other records so that retrospective studies can be done if health concerns are identified in the future.

- ***DoD should continue and further expedite its research efforts on anthrax disease, the organism, and the vaccine.*** Although AVA appears sufficiently effective and safe for use, it is far from optimal. A new vaccine, developed by more modern principles of vaccinology, is urgently needed. An improved vaccine should cause neither severe local reactions (because they may create an unwarranted perception that a vaccine is dangerous even when the effects are transient) nor severe systemic reactions (as expected of all vaccines). Among other characteristics, a new vaccine should require only two or three injections, elicit protection within 30 days that lasts for at least a year, and remain potent for a long period of time so that it can be stockpiled to ensure ample supplies when needed.

For More Information…

Copies of ***The Anthrax Vaccine: Is it Safe? Does it Work?*** are available for sale from the National Academy Press; call (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area), or visit the NAP home page at **www.nap.edu.** The full text of this report is available at **http://www.nap.edu**

Support for this project was provided by the Department of Defense. The views presented in this report are those of the Institute of Medicine Committee to Assess the Safety and Efficacy of the Anthrax Vaccine and are not necessarily those of the funding agencies.

The Institute of Medicine is a private, nonprofit organization that provides health policy advice under a congressional charter granted to the National Academy of Sciences. For more information about the Institute of Medicine, visit the IOM home page at **www.iom.edu.**

COMMITTEE TO ASSESS THE SAFETY AND EFFICACY OF THE ANTHRAX VACCINE

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

WILLIAM E. BARLOW, Senior Scientific Investigator, Center for Health Studies, Group Health Cooperative, and Research Professor, Biostatistics Department, University of Washington

DAN G. BLAZER, J. P. Gibbons Professor of Psychiatry, Duke University Medical Center

LINDA D. COWAN, Professor of Biostatistics and Epidemiology, University of Oklahoma College of Public Health

KATHRYN M. EDWARDS, Professor of Pediatrics, Division of Infectious Diseases, Vanderbilt University School of Medicine

DENISE L. FAUSTMAN, Associate Professor of Medicine, Harvard Medical School, and Director, Immunobiology Laboratory, Massachusetts General Hospital

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

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

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

Consultants

STANLEY A. PLOTKIN, Medical and Scientific Consultant, Aventis Pasteur, and Emeritus Professor of Pediatrics, University of Pennsylvania
GEORGE A. ROBERTSON, Senior Manager of Biological Quality Control, Wyeth-Ayerst Pharmaceuticals

Staff

LOIS JOELLENBECK, Senior Program Officer (Study Director)
LEE ZWANZIGER, Senior Program Officer (until January 2002)
JANE DURCH, Freelance Writer and Editor
TOM BURROUGHS, Freelance Writer
KAREN KAZMERZAK, Research Assistant
PHILLIP BAILEY, Project Assistant
RICHARD MILLER, Director, Medical Follow-up Agency