



Testimony
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Bioterrorism
Preparedness: NIH
Smallpox Research Efforts

Statement of

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Mr. Chairman and Members of the Committee, thank you for inviting me here today to discuss the threat of smallpox as a weapon of bioterrorism and the current efforts by the National Institutes of Health (NIH) to accelerate basic and clinical research related to the prevention and treatment of smallpox.

Recent events, notably the attacks on the World Trade Center and Pentagon and numerous incidents involving the intentional spread of anthrax spores, have highlighted our Nation's vulnerability to attack by bioterrorists. In addition to anthrax, other potential agents of bioterrorism include smallpox virus, the bacteria that cause plague and tularemia, botulinum toxin, filoviruses (e.g. Ebola virus) and arenaviruses (e.g. Lassa virus), and other selected pathogens.

As concern grows about the use of biological agents in acts of terrorism or war, federal health agencies are evaluating and accelerating measures to protect the public from the health consequences of such an attack. The National Institute of Allergy and Infectious Diseases (NIAID), a component of the NIH, supports research on the diagnosis, prevention and treatment of infections caused by a wide variety of pathogens, including those with potential for use as biological weapons.

Our ability to detect and counter bioterrorism depends to a large degree on the state of biomedical science. Basic and applied research supported by NIH complements the efforts of other agencies by developing the essential tools -- diagnostic tests, therapies and vaccines -- needed by physicians, nurses, epidemiologists and other public health workers to prevent and control a disease outbreak.

Smallpox: The Disease

Smallpox, caused by a virus known as *Variola major*, is considered one of the most dangerous potential biological weapons because it is easily transmitted from person to person, and because few people carry full immunity to the virus. Although a worldwide immunization program eradicated smallpox disease in 1977, small quantities of smallpox virus still exist in two secure facilities in the United States and Russia. However, it is possible that unrecognized stores of smallpox virus exist

elsewhere in the world.

The symptoms of smallpox infection appear approximately 12 days (range: 7 to 17 days) following exposure. Initial symptoms include high fever, fatigue, and head and back aches. A characteristic rash, most prominent on the face, arms, and legs, follows in 2-3 days. The rash starts with flat red lesions (a “maculopapular” rash); the lesions evolve at the same rate. Lesions become pus-filled and begin to crust early in the second week. Scabs develop and then separate and fall off after about 3-4 weeks. Individuals are generally infectious to others from the time period immediately prior to the eruption of the maculopapular rash until the time of the shedding of scabs. The mortality of smallpox infection is approximately 30 percent; those patients who recover frequently have disfiguring scars. Smallpox spreads directly from person to person, primarily by aerosolized saliva droplets expelled from an infected person. Contaminated clothing or bed linens also can spread the virus.

Smallpox vaccine has proven to be highly effective in preventing infection. In unvaccinated people exposed to smallpox, the vaccine can lessen the severity of, or even prevent, illness if given within 4 days after exposure. Vaccine against smallpox does not contain the smallpox virus, but rather a laboratory strain of a related virus called vaccinia.

Vaccinations to prevent smallpox have not been required in the United States since 1972. People vaccinated prior to 1972 very likely have diminished immunity to smallpox; people born in the United States after 1972 are not routinely vaccinated. Currently, smallpox vaccination is recommended and available only for individuals who are at risk of imminent exposure, such as laboratory personnel who work with orthopox viruses related to smallpox virus, including vaccinia. No new smallpox vaccine has been manufactured in almost 20 years.

Smallpox Research: Vaccines

The NIAID strategy for smallpox vaccine research is a three-part program that addresses immediate, intermediate, and long-term needs. In the near-term, a bioterrorist attack involving

smallpox would require the utilization of stores of the existing smallpox vaccine. Approximately 15 million doses of the FDA-approved “Dryvax” vaccine have been stored since production stopped in 1983. This clearly would not be enough to respond to a national smallpox epidemic. As a response, NIAID last year initiated a study to determine the feasibility of expanding the use of the existing stores of the Dryvax vaccine by dilution. In this study, investigators examined the skin and immune system responses of normal unimmunized adult volunteers who were given a 1:10 dilution (10 percent) or a 1:100 dilution (1 percent) of off-the-shelf Dryvax vaccine. They compared responses to those from other volunteers who had received the full-strength vaccine. The results showed that the full-strength vaccine had maintained its potency, and that 70 percent of people who received a single dose of the 10-percent vaccine developed a sore followed by a scab at the injection site and antibodies in their blood, indicating protection. Even though the 10-percent vaccine was capable of stimulating an immune response in most people in the study, it is unlikely that it would protect enough people in a large population to sufficiently stop the spread of smallpox. Based on these findings, a new study was designed to determine if a diluted vaccine combined with an alternative vaccination schedule could protect a greater number of people than did the standard dose and regimen.

This study, which will enroll up to 684 people, is evaluating three different doses of Dryvax. Researchers will study the ability of the various vaccine formulations to stimulate a scab, or “take,” at the vaccination site and to produce antibodies in the blood. If participants have not developed a scab in seven to nine days after vaccination, they will be revaccinated with the same vaccine they received the first time. By that strategy, researchers hope to learn which vaccine dose given in a single injection elicits the best response among the largest number of people and whether “boosters” can fortify the immune response in those who did not react to the first vaccination. This study is being conducted at several NIH Vaccine and Treatment Evaluation Units around the United States, including Saint Louis University, Baylor College of Medicine, the University of Maryland, and the University of Rochester. Recruitment of study participants began on Oct. 26, 2001.

NIAID-intermediate-term plans include development of a new smallpox vaccine: a safe, sterile

product grown in cell cultures using modern technology. This vaccine will be rapidly tested in human clinical trials; 250 million doses will be produced and delivered to the federal government by the end of 2002. In the long-term, basic research promises to provide a third generation of smallpox vaccines that could be used in all segments of the population, including pregnant women and people with weakened immune systems. As the research evolves, NIAID continues to be actively involved in the development and testing of new vaccines, including the initiation of clinical trials to determine vaccine safety and efficacy, particularly in special populations.

Therapeutics Research

NIH therapeutics research focuses on the development of new antimicrobials and antitoxins, as well as the screening of existing antimicrobial agents to determine whether they have activity against organisms that might be employed by bioterrorists. For example, in collaboration with DOD, NIH has rigorously screened a large number of antiviral drugs against smallpox and related viruses. One of these agents is an antiviral called *cidofovir*, which is approved by the Food and Drug Administration (FDA) for treating certain AIDS-related viral infections. *Cidofovir* has shown potent activity against smallpox and related viruses in test tube studies and in animal models. NIH has taken the lead in developing a protocol that would allow *cidofovir* to be used in emergency situations for the treatment of smallpox. Concurrently, other anti-smallpox agents are being investigated. NIAID and the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) funded initial screening of approximately 500 compounds for potential antiviral activity against smallpox. Compounds were selected for antiviral testing from the following categories: FDA approved drugs effective against other viruses; antiviral compounds in clinical development for other viruses; known experimental antiviral compounds; and new chemical entities. Several drugs tested in these screening studies, including several *cidofovir* derivatives, have been shown to be active against both *vaccinia* and *cowpox* by *in vitro* evaluation. Promising leads will be further tested with additional *in vitro* studies, animal model testing, or combination therapy studies. In addition, the design of medications active against known drug-resistant

variants of microbes and the development of broad-spectrum agents are important NIH research priorities.

Together with our many research partners, NIH has made substantial progress in the research effort that is critical to our Nation's fight against terrorism. Much remains to be accomplished, however, and the challenges posed by bioterrorism will require a protracted and sustained commitment. With a strong research base, talented investigators throughout the country, and the availability of powerful new research tools, we fully expect that our basic and applied research programs will provide the essential elements that will help enhance our defenses against those who attempt to harm us with bioterrorism.

This concludes my testimony. I would be happy to answer any questions which you or members of the Subcommittee may have.