



Testimony
Before the Committee on Homeland Security,
Subcommittee on the Prevention of Nuclear and
Biological Attack
United States House of Representatives

The NIH Biomedical Research Response
to the Threat of Bioterrorism

Statement of

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Mr. Chairman and Members of the Subcommittee, thank you for the opportunity to discuss with you today the research programs of National Institutes of Health (NIH) aimed at developing effective medical countermeasures against bioterror attacks. The terrible events of September 11, 2001, clearly exposed the vulnerability of the United States to brutal acts of terrorism. The anthrax attacks that followed just a few weeks later made it very clear that the threat of bioterrorism with pathogens or biological toxins represents a serious threat to our Nation and the world.

The Administration and Congress responded forcefully to this threat, and have made biodefense a top national security priority. After a comprehensive review of the Nation's biodefense activities, President Bush in April 2004 signed a Homeland Security Presidential Directive called "Biodefense for the 21st Century" that provides a detailed strategy for defending the Nation from biological attacks. This strategy has four pillars: Threat Awareness; Prevention and Protection; Surveillance and Detection; and Response and Recovery. The NIH was assigned the lead role in the development of medical countermeasures to biological attack, and in the conduct of research concerning potential agents of bioterrorism that directly affect human health. The National Institute of Allergy and Infectious Diseases (NIAID) is the NIH institute with primary responsibility for carrying out this assignment.

In my testimony today I will discuss the NIH biodefense research program, some recent accomplishments in NIH biodefense research, and the mechanisms by which NIH coordinates its activities with other Federal agencies. I will close with a brief discussion of biodefense research to counter possible future threats from engineered microbes, as well as research needed to counter naturally emerging and re-emerging infectious diseases such as influenza.

NIH Biodefense Strategic Plan and Research Agenda

The NIH biodefense research program is guided by a comprehensive strategic planning process. In February 2002, NIAID convened the Blue Ribbon Panel on Bioterrorism and Its Implications for Biomedical Research, whose members were distinguished experts from academic centers, private industry, civilian government agencies, and the military. Three key documents were developed based on this Panel's advice and on extensive discussions with other Federal agencies. These documents are: the *NIAID Strategic Plan for Biodefense Research*, the *NIAID Research Agenda for CDC Category A Agents*, and the *NIAID Research Agenda for CDC Category B and C Priority Pathogens*. Category A agents are the most dangerous microbes and toxins; these agents cause diseases that include anthrax, smallpox, plague, botulism, tularemia, and viral hemorrhagic fevers. These agents were given the highest priority because they: (a) are relatively easily disseminated or transmitted from person to person; (b) result in high mortality rates with the potential for major public health impact; (c) would likely cause significant social disruption; and (d) require special action for public health preparedness. Category B agents are in the second tier of priority. These are agents that: (a) are moderately easy to disseminate, (b) result in moderate morbidity and low mortality, and (c) require specific enhancements of national diagnostic capacity and disease surveillance systems. Category C Agents have the next highest priority. They

include emerging pathogens that could be engineered for mass dissemination in the future because of their availability, ease of production and dissemination, and potential for high rates of morbidity and mortality and major health impact.

The Strategic Plan outlines three distinct priority areas for the biodefense research program: development of *infrastructure* needed to safely conduct research on dangerous pathogens; *basic research* on microbes and host immune defenses; and targeted, milestone-driven *medical countermeasure development* to create the vaccines, therapeutics, and diagnostics that we will need in the event of a bioterror attack. The two biodefense research agendas describe short-term, intermediate, and long-term goals for research on the wide variety of agents that could be used to conduct such an attack. Two recent progress reports describe the significant advances made toward the goals set forth in these research agendas. All these documents are available on the NIAID website at <http://www.niaid.nih.gov/biodefense>.

In addition to NIAID's efforts in biodefense research, in 2004, DHHS tasked the Institute with the development of a research program to accelerate the development and deployment of new medical countermeasures against ionizing radiation for the civilian population. NIAID developed and recently released *The NIH Strategic Plan and Research Agenda for Medical Countermeasures against Radiological and Nuclear Threats*. This *Strategic Research Plan and Agenda* is organized into four sections: (1) basic and translational research on the mechanisms of radiation injury, repair, and restoration that can lead to the identification and characterization of new therapeutics; (2) bioassays and tools for biodosimetry, which will aid in diagnosis; (3) immediate product development of promising therapies; and (4) infrastructure to support the necessary research. The document is intended to unify and strengthen the research community focused on these areas, promote collaboration, and facilitate transition from research to product development. NIH is working closely with DHHS to prioritize the research and development activities in this ambitious agenda within the resources available and as one component of the larger National medical countermeasures research agenda.

Recent Accomplishments

Basic research into the interactions between pathogens and their human hosts provides the foundation for medical countermeasure development. For example, a major NIAID basic biodefense research initiative moving rapidly forward is focused on the human innate immune system, which is comprised of broadly active "first responder" cells and other non-specific mechanisms that are the body's first line of defense against infection. The delineation of methods to boost innate immune responses could lead to the development of fast-acting countermeasures that would be effective against a wide variety of pathogens or toxins that might be used in an attack. In order to develop effective ways to increase innate responses, NIAID-supported scientists at Scripps Institute in La Jolla, CA, are mapping the mechanisms by which innate immunity operates and discerning how these responses are triggered.

NIH biodefense research is ultimately directed toward the development of new and effective medical countermeasures, including vaccines, therapeutics, and diagnostics against potential bioterror agents. Substantial progress in this area already has been achieved. In the area of therapeutics, for example, NIAID-supported scientists recently discovered that a poxvirus infection may be halted by a cancer drug aimed not at the virus, but at the human cellular machinery that the virus needs to spread from cell to cell. Although much work needs to be done on this concept, this research opens the possibility of providing a therapeutic approach to poxviruses such as smallpox and also of circumventing the problem of antiviral drug resistance. This approach might also be applicable to other viruses. Researchers supported by NIAID also are investigating the use of antibodies that can bind to and block the action of toxins produced by the anthrax and botulinum bacteria.

New and improved strategies for the development of vaccines against potential bioterror agents are being pursued vigorously. Our stockpile of usable smallpox vaccines has grown enormously since 2001, when only 90,000 doses were readily available for domestic use. Today, because of clinical research on the minimal dose required to produce immunity and due to an aggressive acquisition program, more than 300 million doses are held in the Strategic National Stockpile (SNS). Moreover, NIAID-supported researchers are testing next-generation smallpox vaccines that may prove to be effective against the smallpox virus and safer than the current smallpox vaccines, thus potentially allowing them to be used by populations that have contraindications for currently available smallpox vaccines, including people with weakened immune systems. One of these vaccine candidates, modified vaccinia Ankara (MVA), is based on a strain of the vaccinia virus that causes fewer side effects than the traditional Dryvax vaccinia virus strain because it does not replicate effectively in human cells. Human trials of MVA vaccines are underway at NIH and elsewhere. Encouragingly, vaccine manufacturers Bavarian Nordic and Acambis announced this year that Phase I and Phase II trials have demonstrated MVA vaccine to be safe and immunogenic in human volunteers, complementing earlier studies by NIAID intramural scientists and their colleagues showing that MVA protects monkeys and mice from smallpox-like viruses. Additionally, NIAID supports a targeted research program to reduce the incidence and severity of eczema vaccinatum (EV), the most common life-threatening complication of smallpox immunization, and to protect individuals with atopic dermatitis from the adverse consequences of vaccinia exposure. The Atopic Dermatitis and Vaccinia Immunization Network conducts research that will identify and evaluate ways to reduce the risk of EV.

NIAID also has made progress in the development of a vaccine to protect against viral hemorrhagic fever viruses that could potentially be used as bioterror agents. For example, research scientists at the NIAID Vaccine Research Center have completed enrollment of a Phase I human trial of a DNA-based vaccine for Ebola. Thus far, the vaccine appears to be safe and immunogenic.

NIAID also has played a major role in the rapid development of the next-generation anthrax vaccine known as recombinant protective antigen, or rPA. The technology for

creating this vaccine was developed at the United States Army Medical Research Institute for Infectious Diseases (USAMRIID), and NIAID has supported its advanced research and development. Clinical trials to evaluate rPA in healthy adults currently are underway. Preliminary unpublished data suggest that the immune responses elicited in humans are similar to those elicited in animal studies. Those animal studies have demonstrated that the rPA vaccine protected animals against aerosol challenge with anthrax spores. Last November, the Department of Health and Human Services (DHHS) awarded a contract for the acquisition of 75 million doses of rPA vaccine to be held in the SNS. NIAID's rPA product development initiatives were instrumental in making the initiative possible. Candidate vaccines for plague, botulinum toxin, and other agents are also under development.

In addition to conducting and supporting biodefense research initiatives, NIH has invested in several research infrastructure expansion programs. NIAID has established a nationwide network of Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research (RCEs). These Centers are now conducting fundamental research on infectious diseases that could be used in bioterrorism; developing diagnostics, therapeutics and vaccines needed for biodefense; and providing training for future biodefense researchers. Two new RCE awards were announced on June 1, 2005, bringing to ten the total number of RCEs nationwide. NIAID also supports five Cooperative Centers for Translational Research on Human Immunology and Biodefense to characterize human immune responses to disease-causing organisms, develop technologies to measure these responses, and apply this knowledge to design therapies that strengthen host immunity. In addition, NIAID supports the construction of two National Biocontainment Laboratories (NBLs), built to Biosafety Level 4 standards and therefore capable of safely containing any known pathogen, and nine Regional Biocontainment Laboratories (RBLs) with Biosafety Level 3 facilities. NIAID also will support the construction of two additional RBLs this year. Together, these high-level research laboratories, some of which are already under construction, will provide the facilities needed to carry out the Nation's expanded biodefense research program with the highest degree of safety and security.

Coordination of NIH-Supported Medical Countermeasures Research

Although NIH is a leading agency in government-sponsored research to develop medical countermeasures against biological threats, it is by no means the only agency involved; the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Department of Defense (DoD), the Department of Homeland Security (DHS), the Department of Agriculture (USDA), and other governmental organizations also play important roles. Coordination among the various agencies involved is therefore extremely important. In broad terms, Federal medical countermeasures research is coordinated at three distinct levels: within NIH, within DHHS, and across the government as a whole.

Within NIH. Although NIAID is responsible for the majority of NIH-sponsored medical countermeasures research for infectious agents and toxins, other NIH Institutes and Centers make significant contributions. The focal point for trans-NIH coordination and planning of all medical countermeasure research activities in these areas is the NIH Biodefense Research Coordinating Committee. I am Chairman of this committee, which meets at least quarterly. It is administered by the NIAID Office of Biodefense Research, which also serves as the liaison office for NIH contacts with other Federal agencies such as DoD and DHS.

Within DHHS. Coordination of medical countermeasures research between the CDC, NIH, FDA, and other agencies within DHHS is the responsibility of the DHHS Office of Public Health Emergency Preparedness (OPHEP). The OPHEP Office of Research and Development Coordination holds periodic meetings with all governmental stakeholders in the development of medical countermeasures.

Across Federal Agencies. At the highest level, coordination of medical countermeasures research is carried out by the White House, and in particular, the Homeland Security Council, the National Security Council, and the Office of Science and Technology Policy. The focal point for interagency efforts to establish U.S. Government requirements and prioritize and coordinate medical countermeasures acquisition programs is the Weapons of Mass Destruction Medical Countermeasures (WMDMC) Subcommittee ("WMDMC Subcommittee"). This interagency subcommittee of the National Science and Technology Council is co-chaired by DHHS, DHS, and DoD and draws stakeholders from throughout the Federal government.

Although these three levels describe the structure through which biodefense research programs are formally coordinated, NIH collaborates daily with the other Federal agencies and is party to a large number of interagency programs, informal contacts, and communication mechanisms that significantly contribute to the efficiency and effectiveness with which medical countermeasures research is carried out across the U.S. Government. For example, my staff meets regularly with the Defense Threat Reduction Agency and the Defense Advanced Research Projects Agency, two important entities within the research infrastructure in the DOD. NIH biodefense staff also work closely with the research community at Fort Detrick and the United States Army Medical Research and Materiel Command. Moreover, NIH is a major participant

in the National Interagency Biodefense Campus now under construction at Fort Detrick; once complete, this facility will foster improved coordination and synergy in Federal biodefense activities.

Emerging Engineered and Natural Threats

Looking toward the future, it is clear that as the power of biological science and technology continues to grow it will become increasingly possible that we will face an attack with a pathogen that has been deliberately engineered for increased virulence. This enhanced virulence could take the form of resistance to one of more antibiotic or antiviral drugs, increased infectiousness or pathogenicity, or, in the somewhat longer term, a new virulent pathogen made by combining genes from more than one organism. Ongoing research to counter these threats includes the development of new broad spectrum therapies, new vaccines with broad cross-reactivity, and immunomodulators to make drugs and vaccines more effective.

Threats arising from deliberate human action are not the only dangers we will confront, because naturally occurring infectious diseases such as HIV/AIDS, SARS, and West Nile virus emerge or re-emerge on a regular basis. A current example is the H5N1 avian influenza virus, which has killed millions of wild and domestic birds, as well as more than 50 people in four countries (Thailand, Vietnam, Cambodia, and Indonesia). There have been two likely cases of human-to-human transmission of the H5N1 virus, and it is possible that other such transmissions have occurred recently. It is also possible that the H5N1 virus, through genetic mutation or recombination with a human-adapted influenza virus, could become easily transmissible among people. Given the poor condition of public health systems in many underdeveloped regions and the speed of modern air travel, the consequences of such an event would be severe.

Although a pandemic alert has not yet been declared, NIAID has taken a number of steps to develop and clinically test vaccines against H5N1 influenza. In January 2004, researchers at St. Jude Children's Research Hospital obtained a clinical isolate of a highly virulent H5N1 virus and used a technique called reverse genetics to create an H5N1 vaccine candidate from this strain. NIAID then contracted with Sanofi-Pasteur and Chiron Corporation to manufacture pilot lots of eight and ten thousand vaccine doses, respectively. The inactivated H5N1 vaccines will be tested in Phase I and II clinical trials that will assess safety and the appropriate vaccine dosage to optimize immunogenicity, as well as provide information about how the immune system responds to this vaccine. The Sanofi-Pasteur trial, which began on April 4 and is fully enrolled, is testing the vaccine in approximately 450 healthy adults. Trials of the Chiron-produced vaccines are expected to begin later this year.

In addition to these relatively small pilot lots, DHHS contracted with Sanofi-Pasteur to produce two million doses of its H5N1 vaccine, in order to ensure that the manufacturing techniques, procedures, and conditions that would be used for large-scale production will yield a satisfactory product. Moving to large-scale production of the vaccine in parallel with clinical testing of pilot lots is an unusual step, and an indication of the urgency with which we have determined that H5N1 vaccine

development must be addressed. Waiting for the results of the initial clinical trials, which would be the normal procedure, would delay our ability to make large quantities of vaccine by at least six months. These doses, which have now been manufactured, could be used to vaccinate health care workers, researchers, and, if indicated, the public in affected areas.

Antiviral medications are an important counterpart to vaccines as a means of controlling influenza outbreaks, both to prevent illness after exposure and to treat infection after it occurs. Efforts are underway to test and improve antiviral drugs to prevent or treat H5N1 influenza. Researchers recently determined that H5N1 viruses are sensitive to oseltamivir, a neuraminidase inhibitor that is marketed as Tamiflu and is approved for individuals older than one year. DHHS has deposited approximately 2.3 million treatment courses of oseltamivir in the SNS, to which it is anticipated that more doses will be added. Scientists are planning to conduct studies to further characterize the safety profile of oseltamivir for very young children; other studies are in progress to evaluate novel drug targets, as well as long-acting next-generation neuraminidase inhibitors. In addition, development and testing in animals of a combination antiviral regimen against H5N1 and other potential pandemic influenza strains is underway.

NIAID also is developing vaccines that are potentially protective against SARS and West Nile virus. NIAID scientists at the Vaccine Research Center have completed enrollment for a Phase I trial of a recombinant SARS DNA vaccine, and have initiated a Phase I clinical trial of a DNA West Nile virus vaccine.

In conclusion, it is clear that defense against biological threats, whether natural or the result of deliberate human action, will of necessity continue to be a high national security priority for the foreseeable future. As per the President's Homeland Security Presidential Directive 10, "Biodefense in the 21st Century," NIH is taking the lead in the construction of a sustainable and comprehensive program to develop medical countermeasures for biological threat agents. The long institutional experience that NIAID has had with infectious disease research allowed us to rapidly take on a greatly expanded role in civilian biodefense after the terrorist attacks in the fall of 2001, and I am confident that we are making good progress.

I appreciate this opportunity to appear before you today, and I would be pleased to answer any questions that you may have.