



**Testimony
Before the Committee on Government Reform
United States House of Representatives**

**NIH's Biomedical Research
Response to Influenza and
Other Emerging and
Re-emerging Infectious Diseases**

Statement of

Anthony S. Fauci, M.D.

Director

National Institute of Allergy and Infectious Diseases

National Institutes of Health

U.S. Department of Health and Human Services



For Release on Delivery
Expected at 10:00AM
on Thursday, February 12, 2004

Introduction

Mr. Chairman and Members of the Committee, thank you for the opportunity to discuss with you the role of the National Institutes of Health (NIH) in combating influenza and other emerging and re-emerging infectious disease threats. Responding effectively to the challenges posed by diseases such as influenza, SARS, West Nile virus, or HIV requires a multi-faceted, coordinated and focused approach with close collaboration between public health authorities, health care delivery systems, the pharmaceutical industry, and the biomedical research community. The National Institute of Allergy and Infectious Diseases (NIAID), a component of NIH, is the lead Federal agency for conducting, supporting, and coordinating research on influenza and other infectious diseases. As such, NIAID plays a key role in our national effort to prepare for and to respond robustly to the threat of influenza and other emerging infectious diseases.

Emerging and Re-emerging Infectious Diseases

Infectious diseases have afflicted humanity since ancient times, and they will continue to confront us as long as man and microbes co-exist. Unfortunately, the viruses, bacteria, and parasites that cause infectious diseases do not remain static, but continually and dramatically change over time as new pathogens emerge and as familiar ones (such as influenza) re-emerge with new properties or in unfamiliar settings. Such emerging and re-emerging infections have shaped the course of human history while causing incalculable misery and death. For example, importation of smallpox into Central America caused 10-15 million deaths in 1520-1521, effectively ending Aztec civilization. The emerging disease, AIDS, first recognized in 1981, now threatens to surpass in global fatality the plague pandemic of the 14th century and the influenza pandemic of 1918-1919—two other emerging infections that each killed tens of millions of people.

In the past five years alone we have witnessed the introduction of West Nile and monkeypox viruses in the United States, as well as the emergence of a new infectious disease, SARS. In addition, we were confronted in 2001 with a third category of threat, a disease resulting from the deliberate release of an infectious agent, in the form of the anthrax bioterrorist attacks in the United States. Today, we are concerned about sudden outbreaks of diseases such as anthrax, smallpox, and plague not because we expect them to re-emerge naturally, but because they could be released by deliberate human action. Our ability to respond effectively to new infectious disease threats, whether they are emerging, re-emerging, or deliberately introduced, involves many different kinds of activities and many different organizations. From a public health perspective, surveillance and response are the key elements in controlling emerging infections and depend upon rapid detection and containment of pathogens in populations and the environment. Globally, such efforts are coordinated by the World Health Organization (WHO), which recently led the successful effort to contain last year's global SARS outbreak. In the United States, such efforts are led by the Centers for Disease Control and Prevention (CDC), which along with state and local health departments and other agencies recently have made significant strides in national disease surveillance and response capacity. Physicians, nurses, other health care workers and hospitals also must be integrated to respond in a coordinated manner to an outbreak, and the pharmaceutical industry must be fully engaged to develop and manufacture needed diagnostic tools, therapeutics, and vaccines. Within the Department of Health and Human Services (HHS), NIH, CDC, the Food and Drug Administration (FDA), and other agencies all have distinct but complementary roles to play, and have a long history of cooperation. The NIH concentrates on a strong and

focused research program that is critical to preventing and controlling these infectious disease threats.

The conduct, support, and coordination of basic, translational, and applied infectious disease research is the primary responsibility of NIAID. First and foremost, NIAID supports basic and clinical research, which is needed to understand how pathogens cause disease. These research efforts include understanding how microbes replicate, how disease spreads, and what factors lead them to cause serious illness or death. Of particular importance is the understanding of how the body's protective mechanisms, i.e. the immune system, protect against the devastating effects of microbial invaders. In addition, NIAID works closely with academic and industrial partners to translate basic and clinical research findings into new diagnostic tools, therapeutics, and vaccines. This translational and applied research effort also involves close coordination with FDA, CDC, and other Federal agencies to ensure that new countermeasures move as efficiently as possible from the laboratory into general use.

After the anthrax attacks of 2001, Congress dramatically increased funding for biodefense research, much of which was directed to NIH, and to NIAID in particular. NIAID's long institutional experience with infectious disease research of all kinds allowed us to seamlessly take on a greatly expanded biodefense role. Virtually all the fruit of NIAID biodefense activities—including research results, intellectual capital, laboratory resources, and countermeasures in the form of diagnostics, therapeutics, and vaccines—will apply to emerging, re-emerging, and deliberately released microbes alike; recent experience tells us that knowledge developed to understand one pathogen invariably applies to others. For example, when HIV first emerged, antiviral drug development was in its infancy; however, new technologies, many of which were

pioneered at NIAID, have led to the development of more than 20 antiretroviral drugs that can effectively suppress HIV replication and dramatically reduce AIDS morbidity and mortality. These same technologies, and the lessons learned about antiviral drug development, are now being applied to the development of new generations of drugs against many viruses, including influenza, SARS, smallpox, and Ebola.

Influenza Research Activities at NIAID

Influenza can be viewed as a classic example of a re-emerging disease; it is not a new disease, but it continually changes. In most years, influenza viruses that typically infect humans globally undergo small changes in the properties of their surface proteins. If enough of these changes accumulate, the virus is able to escape the human immune response that was primed by prior exposure to influenza viruses or vaccination. This is referred to as “antigenic drift” and it is the basis of well-recognized patterns of influenza disease that occur every year, which nonetheless cause significant mortality and morbidity. In the United States, influenza infections over the past 10 years have resulted in an average of 36,000 deaths and 114,000 hospitalizations each year, and the WHO estimates that the annual average number of deaths worldwide is approximately 500,000. Although only three types of influenza viruses routinely circulate among humans, all known influenza A subtypes are endemic in the gastrointestinal tract of wild ducks. Because the replication machinery of the influenza virus is error prone, as the virus multiplies, avian influenza viruses can emerge that may be able to jump species into domestic poultry, farm animals such as pigs, and humans. This type of significant change in the antigenic makeup of the virus is referred to as “antigenic *shift*”. When an influenza virus jumps species from an animal such as a chicken to a human, it usually is a “dead end” infection in that the virus cannot readily transmit further from human to human.

Avian influenza viruses made the jump directly from birds to humans in 1997, but because the virus did not acquire the ability to spread from human to human, only a limited number of deaths (6 out of 18 confirmed cases) occurred. Currently, H5N1 avian influenza viruses in Vietnam and Thailand also have made the jump directly from birds to humans and have resulted in deaths of 18 out of 23 confirmed cases (as of February 9) representing a 78% mortality rate. The fear is that the avian H5N1 and another human influenza virus such as H3N2 might recombine if they were to simultaneously co-infect a person, resulting in the global spread of a new deadly and transmissible human influenza virus referred to as a pandemic strain.

Deadly pandemics are known to have occurred in 1918, 1957, and 1968. The pandemic that occurred in 1918-1919 after an antigenic shift killed 20-40 million people worldwide, including more than half a million in the United States. The pandemics that occurred following other shifts in the virus in 1957 and 1968 killed approximately 2 million and 700,000 people worldwide, respectively. This explains our current high level of concern about the appearance of new forms of virulent H5N1 avian influenza viruses in Asia, which could subsequently recombine with human influenza viruses and result in another pandemic. 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, should it result in an influenza pandemic, would be severe.

The overall goal of the Influenza Program at the NIAID is to support research that leads to more effective approaches to controlling influenza virus infections. This program has two major components, both of which are specified in the nation's draft Pandemic Influenza Preparedness and Response Plan. The first component reflects longstanding programs for interpandemic influenza—research to understand the pathogenesis,

transmissibility, evolution, epidemiology, and the immune response to influenza viruses. These interpandemic research areas include:

- **Basic Research.** NIAID supports many basic research projects aimed at understanding how the influenza virus replicates, interacts with the host, stimulates an immune response and evolves into new strains. Results from these studies lay the foundation for the design of new antiviral drugs, diagnostics, and vaccines.
- **Antiviral Drugs.** NIAID currently supports the identification, development and evaluation of new antivirals against influenza including the screening of new drug candidates to see if they have activity against virus both in laboratory cells and in animals. We also are developing novel broad-spectrum therapeutics intended to work against many influenza virus strains; some of these target viral entry into human cells, while others specifically attack and degrade the viral genome. Development and evaluation of a combination antiviral regimen against potential pandemic influenza strains is also now under way.
- **Diagnostics.** NIAID supports the development of rapid, ultra-sensitive devices to detect influenza virus infection. Although early in development, these devices will allow detection of newly emerging viral mutants and discrimination between different antigenic sub-types.
- **Vaccines.** Because influenza is so easily transmitted, effective vaccines are essential to the control of annual influenza epidemics. The current

egg-based system used to produce licensed influenza vaccines—despite being reliable for more than 40 years—can be improved. Limitations of the current system include: (1) a lengthy manufacturing process; (2) the need to select which virus strains will be in the vaccine at least six months in advance of the influenza season; (3) the need to produce nearly 90 million doses of a new influenza vaccine each year; and (4) the requirement of hundreds of millions of fertilized chicken eggs to manufacture the vaccine. This early decision about which strains to include in the influenza vaccine will not always be correct, and the long lead time required to produce the vaccine makes mid-stream corrective action impossible. Additional limitations could include allergenicity of eggs in some individuals and inability to use eggs for propagation of viruses lethal to chickens.

NIAID is currently supporting several research projects aimed at developing vaccines that can be manufactured more rapidly, are more broadly cross-protective, and are more effective. The use of reverse genetics—a genetic tool developed by NIAID-supported scientists—holds the promise for more rapid generation of high-yielding vaccine candidates that match the anticipated epidemic strain. Reverse genetics also can be used to turn highly pathogenic influenza viruses into vaccine candidates more suitable for vaccine manufacturing by removing or modifying certain virulence genes; laboratories around the world are using the technique to prepare vaccine candidates against the H5N1 viruses emerging in Asia because of the difficulty of using the traditional production methods in eggs. NIAID also is funding the development of new influenza vaccine

technologies. Recently, the NIAID supported a Phase II clinical trial of a new influenza vaccine produced in a cell culture system as an alternative to manufacturing the vaccine in eggs. Another approach has focused on improving the effectiveness of current inactivated vaccines by giving increasing doses of influenza vaccine to elderly individuals, the population which frequently accounts for up to 90% of the influenza deaths each year in the United States. NIAID also is funding the development of new technologies for the production of influenza vaccines. These include DNA-based approaches and broadly protective vaccines based on influenza virus proteins that are shared by multiple strains of the influenza virus. Because NIAID has had remarkable success in the past with ground breaking vaccine research—including advances that led to hepatitis B, *Haemophilus influenzae b*, pneumococcal pneumonia, and acellular pertussis vaccines, as well as the new live attenuated intranasal influenza vaccine approved by the FDA last year—I am confident that one of the approaches we are pursuing also will lead to a useful, “next-generation” influenza vaccine that can easily be adapted to emerging influenza strains.

- **Surveillance and Epidemiology.** The threat from influenza, like virtually all emerging and re-emerging infectious disease threats, is global in scope. For this reason, NIAID has expanded its activities in other countries in recent years. Through a contract for pandemic influenza preparedness, NIAID supports a long-standing program in Hong Kong to detect the emergence of influenza viruses with pandemic potential in animals. Under this program, Dr. Robert Webster of St. Jude Children's

Research Hospital in Memphis, Tennessee, leads a group that detected the re-emergence of highly pathogenic H5N1 avian strains in this area in 2002 and 2003, and was instrumental in the early detection and characterization of the SARS coronavirus in 2003. This underscores the concept that research on one type of infectious disease often supports or can be applied to research on the other types of infectious diseases, whether newly emerging, re-emerging, or deliberately introduced.

The second component of NIAID's Influenza Program is geared at addressing the emergence of influenza viruses with pandemic potential in humans. After a pandemic influenza strain emerges and a Pandemic Alert has been declared, the draft U.S. Pandemic Influenza Preparedness and Response Plan describes specific roles for NIAID. Foremost among these is to help develop and produce an effective vaccine as rapidly as possible. NIAID would assist in the characterization of the newly emerging influenza strain, create vaccines candidates, develop investigational lots of candidates, and produce and distribute research reagents for use by vaccine researchers in academic and pharmaceutical industry laboratories. NIAID would also work with industry to produce and clinically test candidates at different doses and in different populations in our vaccine clinical trials sites and would coordinate closely with CDC, FDA, and WHO to ensure that a safe and effective vaccine is available to the public as soon as possible. NIAID-supported scientists will also evaluate the susceptibility of the newly emerging virus to the currently available influenza drugs and new drug candidates.

Conclusion

Mr. Chairman, thank you again for allowing me to discuss NIH's efforts to address the threat of influenza. In addition to the significant toll exacted by influenza each year in the United States, the risk of pandemic influenza is significant and the consequences could be very serious. Influenza, however, is one among many ever-changing infectious disease threats confronting our nation and the world that have serious adverse health and economic impact. Fortunately, much of what we learn from the study of one pathogen can often be applied to others. As I have described for you today, NIAID, as the lead Federal agency for infectious disease research, constantly strives to improve our ability to respond to any infectious disease threat, whether emerging, re-emerging, or deliberately introduced by man.

I would be pleased to answer your questions.