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The Role of NIH-Supported Research in the Response to 2009-H1N1 Influenza

Statement of

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Mr. Chairman and members of the Subcommittee, thank you for the opportunity to discuss the NIH research response to the public health threat that the Nation and world face with regard to outbreaks of the novel 2009-H1N1 influenza A virus, which was initially referred to as “swine flu.”

Over the past several years, the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH) within the U.S. Department of Health and Human Services (HHS), has conducted a major research effort that builds on long-standing programs related to seasonal influenza in order to improve our preparedness for pandemic influenza. Although we have focused a good deal of attention recently on H5N1 avian influenza, it always has been clear that the next pandemic threat could come from another influenza virus altogether.

That threat is now upon us. In response, NIH has closely reviewed the research agenda that underpins the development of countermeasures for all influenza subtypes, but the 2009-H1N1 in particular. NIH plans to invest more than $200 million in various types of influenza research, including H1N1 this fiscal year.

In my remarks today, I will outline what is known about the basic biology of this virus and discuss the research response being mounted by NIH that is synergistic with—and complementary to—the efforts of other components of HHS such as the Biomedical Advanced Research and Development Authority, and in particular of our sister agencies, the Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA), as well as other organizations around the world.

Seasonal and Pandemic Influenza

Influenza viruses affect many animal species, including birds, pigs, and humans. As influenza viruses circulate, the genes that determine the structure of their surface proteins undergo small changes called mutations. These discrete mutations accumulate to cause a gradual “antigenic drift” that allows an influenza virus in a typical influenza season to substantially evade immunity that was developed from prior exposure to influenza viruses or from vaccination. Antigenic drift in human influenza viruses is the basis for the predictable patterns of seasonal influenza seen in most years and is the reason that we annually reassess the strains to be included in the seasonal influenza vaccine.

In humans, seasonal influenza epidemics in the Northern hemisphere usually occur in winter months. These seasonal events cause symptomatic illness in 15 to 60 million people in the United States every year; they result in an average of about 200,000 hospitalizations and 36,000 deaths. With seasonal influenza, some residual or background immunity may exist in the population due to prior exposure or vaccination. This background immunity tempers the number of illnesses, hospitalizations, and deaths we see every year. Most of the severe

outcomes from seasonal influenza occur among people aged 65 years and older, in very young children, and those with chronic health conditions. Globally, seasonal influenza causes 3 million to 5 million cases of severe illness each year, and an estimated 250,000 to 500,000 influenza-related deaths, according to the World Health Organization.

Influenza viruses also can undergo more extensive changes that lead to what is called an "antigenic shift," and these can pose a more serious threat to human health. One way antigenic shifts occur is through humans acquiring a novel influenza virus from a non-human source. For example, influenza viruses infecting birds can, on rare occasions, also infect humans. Although the result is usually a "dead-end" infection that does not spread further, the virus might undergo mutations that allow limited human-to-human transmission. Once transmission begins, further mutation can make human-to-human transmission more efficient and sustainable. Another way that antigenic shifts occur is through a process called reassortment, in which two virus strains co-infect a host and exchange genes. Whatever the mechanism, the result may be the evolution of a new virus to which the human population has little or no immunity. If this new virus is able to efficiently transmit from human to human, then an influenza pandemic may result. Pandemic influenza is an unpredictable and rare event that can occur at any time of year.

In the 20th century, influenza pandemics occurred three times—in 1918, 1957, and 1968. The pandemics of 1957 and 1968 were serious infectious disease events that killed approximately two million and 700,000 people worldwide, respectively. The 1918-1919 pandemic, however, was catastrophic: epidemiologists estimate that it killed more than 50 million people worldwide, including more than 500,000 people in the United States, and caused enormous social and economic disruption.

Given this history, we long have expected that a new influenza virus would emerge and another pandemic would occur. As you know, the U.S. Government, and HHS in particular, has been preparing for an influenza pandemic for a number of years. These efforts were bolstered after H5N1 avian influenza reemerged in Southeast Asia in 2003. U.S. Government pandemic preparedness plans assign to the NIH the primary responsibility for scientific research and clinical trials needed to develop and test pandemic influenza vaccines and therapies.

NIH long has supported basic influenza research to understand better how influenza viruses replicate, interact with their hosts, stimulate immune responses, and evolve into new strains. Results from these basic research studies lay the foundation for the design of new antiviral drugs, diagnostics, and vaccines, and are applicable to seasonal epidemic and pandemic strains alike. NIH has worked with our partners in the biotechnology and pharmaceutical industries to speed

development of new influenza vaccines, diagnostic tools, and anti-influenza drugs. We also have built a substantial infrastructure of research centers, NIH intramural and NIH-supported extramural laboratories, highly trained personnel, and clinical research networks to rapidly conduct research should a virus with pandemic potential emerge.

A virus with clear pandemic potential, the 2009-H1N1 influenza virus, has now emerged. NIH is fully engaged in an accelerated effort to understand this virus and rapidly develop countermeasures. Scientists already have learned a great deal about the biology of the 2009-H1N1 virus, and we are taking all possible steps to learn more. NIH also is fully engaged in carrying out its mandate in developing vaccines and testing therapeutics to counter this newly emerged viral threat.

Basic Science

Scientists at CDC, FDA, NIH, NIH-supported laboratories, and elsewhere around the world have obtained samples of the 2009-H1N1 virus from the CDC. The complete genome sequences of numerous viral isolates already have been determined. Our studies tell us that this is a very unusual virus: its particular genetic combination of influenza virus segments has not been recognized before in the United States or elsewhere. As you know, the new 2009-H1N1 strain has been infecting humans. Although it is clear that the virus can be transmitted from one person to another, it is not yet known precisely how efficient transmission is. We also are now aware that pigs can become infected with the virus as well. Research is ongoing to understand the precise circumstances surrounding the origin of this strain.

When news of the emergence of 2009-H1N1 influenza first broke, NIH immediately began a thorough and rapid characterization of the virus in cell culture and laboratory animals in addition to participating with HHS agencies in assessing the immediate needs for further investigation. That effort includes intramural researchers on the NIH campus, researchers in preexisting NIH research networks such as the Centers of Excellence in Influenza Research and Surveillance (CEIRS) and Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases (RCEs), as well as industry partners and individual NIH grantees. We anticipate that these efforts will rapidly yield important information; for example, which animals the virus can infect, the mechanisms by which the virus causes disease, the viral molecular signatures of virulence and enhanced transmission, and the major viral and host factors important in mounting an immune response to the virus. NIH also has developed clinical protocols in New York and Texas to collect clinical samples from patients with 2009-H1N1, and the NIH Clinical Center has geared up to accept patients for participation in research protocols—should that be necessary. These and other anticipated clinical studies will provide crucial information about how the virus behaves in humans, how the human immune system responds to it, and how

much cross-protection, if any, is provided by antibodies to previously circulating human H1N1 viruses.

Vaccines

Generation of viral seed stocks in preparation for developing a vaccine against the 2009-H1N1 virus is proceeding rapidly. Making full use of our multifaceted research infrastructure, we are now working with our partners at HHS and in industry on the next stages in the multistep process of developing a vaccine against this novel virus.

Two types of vaccines are currently licensed for use in the United States. Inactivated vaccines are based on chemically killed influenza viruses and are injected intramuscularly. Live, attenuated vaccines are based on a weakened influenza virus engineered to contain the hemagglutinin and neuraminidase genes of a circulating influenza strain and are given as a nasal spray. Both require culture of virus in chicken eggs. The first step in creating both kinds of vaccines, now underway in CDC, FDA, private sector, and NIH-supported laboratories, is the development of virus reference strains suitable for use in manufacturing. These seed viruses will then be used by manufacturers to produce pilot vaccine lots suitable for testing in humans. NIH will use its longstanding vaccine clinical trials infrastructure—notably our network of Vaccine and Treatment Evaluation Units—to quickly evaluate pilot lots of vaccine candidates to determine whether the vaccine is safe, its ability to induce protective immune responses, and the appropriate dose and number of dosages. All systems are “go” for this stepwise process.

Adjuvants are additives that help create a more vigorous immune response to a vaccine, thereby reducing the amount of antigen required per vaccine dose. Results from clinical trials of candidate pre-pandemic avian influenza vaccines indicate that one adjuvant increases the immune response and could reduce the required dose. This adjuvant may be clinically evaluated in a 2009-H1N1 vaccine, and several other adjuvants are currently under development as well, but vaccines containing these novel adjuvants are not currently licensed in the United States.

NIH and its industry partners have been developing several other kinds of influenza vaccines that are not yet licensed for use. These include recombinant DNA technologies that yield subunit vaccines, in which various influenza virus proteins are selectively grown in cultured cells that are then purified and used in a vaccine; DNA vaccines, in which harmless influenza genetic sequences are injected directly into a person to stimulate an immune response against the proteins coded for by these genetic sequences; and approaches that insert the genes of influenza virus into a different, harmless virus (a “vector”) that is used as a vaccine. Studies to create prototype 2009-H1N1 influenza vaccines that rely on these experimental strategies are underway. However, because these

"next-generation" vaccines will require additional safety and efficacy testing before they can be deployed, they are unlikely to reach the public before the more traditional types of vaccines described above.

Antiviral Therapies and Diagnostics

Antiviral medications are an important counterpart to vaccines as a means of controlling influenza, for treating infection after it occurs and, under certain circumstances, for preventing infection prior to or immediately after exposure. Although the 2009-H1N1 virus is sensitive to oseltamivir (Tamiflu®) and zanamivir (Relenza®), experience tells us that resistance to influenza antiviral medications frequently emerges. Indeed, over the past two years the circulating seasonal H1N1 influenza viruses have become oseltamivir-resistant, even while other influenza viruses have remained sensitive to the drug.

In recent years, NIH has been working to develop and test the next generation of influenza antivirals. Three drugs are now in clinical testing, including a long-acting neuraminidase inhibitor, an inhibitor of the enzyme that replicates viral genes, and a drug that prevents the virus from entering human lung cells. We will soon begin to evaluate how well these candidate antiviral drugs block the 2009-H1N1 strain and to screen other compounds for activity against the virus.

Improved methods of diagnosing 2009-H1N1 influenza infection at the point of care would be of substantial value in the months ahead, helping to differentiate people with the new influenza strain from those with other conditions who present with similar symptoms. Prompt and precise point-of-care diagnosis would help slow spread of the virus and maximize the efficiency with which stockpiled antivirals are used. NIH has been developing diagnostic platforms capable of rapidly identifying a wide variety of pathogens in clinical samples, including specific subtypes of influenza, and we are now working to accelerate development of these platforms to provide improved diagnostics for 2009-H1N1.

Shared Research Resources

When infectious diseases emerge, NIH serves an important role in providing materials, support, and expertise to researchers and the public health community. These resources include blood samples from infected patients, immunological assay reagents, animal models, genomic sequencing and information resources, and isolates of the virus.

NIH intramural and extramural researchers, in turn, depend on materials and information shared by CDC, FDA, and other public health agencies around the world. For example, CDC provided NIH intramural and NIH-supported researchers with samples of the 2009-H1N1 virus, while NIH is making available to CDC researchers archived blood samples from people vaccinated in the 1976 swine influenza outbreak as well as influenza reagents from an NIH research

reagent repository. From my perspective, the coordination and cooperation between government agencies, and with private industry, has been outstanding.

Conclusion

It is important to recognize that we are only in the earliest stages of understanding how the 2009-H1N1 influenza virus emerged and what impact it might have. Influenza viruses are highly unpredictable, and it is unwise to make predictions about how a virus might behave in the future. For example, although the virus at this time has caused mostly relatively mild disease in this country, we do not know whether that might change in the coming months. Nor do we know whether the virus will become resistant to the antiviral drugs we have stockpiled. In short, we simply cannot predict at this time whether the emergence of the 2009-H1N1 virus will prove to be a relatively limited event, or whether it could develop into a major global pandemic either in the immediate future or during a period of seasonal influenza. The NIH and other government agencies are acting to prepare for any possibility.

Our ongoing, collective efforts to prepare for an influenza pandemic—with research, vaccine manufacturing infrastructure, antiviral drugs, public health measures, efficient infection control, and clear public communication—have given us a valuable advantage in the serious situation we face today. I very much appreciate the support that Congress has provided over the years to achieve this level of preparedness.

I would be pleased to answer any questions you may have.