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PANDEMIC INFLUENZA: PROGRESS MADE AND CHALLENGES AHEAD

HEARING

BEFORE A

SUBCOMMITTEE OF THE

COMMITTEE ON APPROPRIATIONS

UNITED STATES SENATE

ONE HUNDRED TENTH CONGRESS

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PANDEMIC INFLUENZA: PROGRESS MADE AND CHALLENGES AHEAD

WEDNESDAY, JANUARY 24, 2007

U.S. SENATE,
SUBCOMMITTEE ON LABOR, HEALTH AND HUMAN SERVICES, AND EDUCATION, AND RELATED AGENCIES,
COMMITTEE ON APPROPRIATIONS,
Washington, DC.

The subcommittee met at 9:50 a.m., in room SD–124, Dirksen Senate Office Building, Hon. Tom Harkin (chairman) presiding.

Present: Senators Harkin, Reed, Durbin, and Specter.

OPENING STATEMENT OF SENATOR ARLEN SPECTER

Senator SPECTER. Good morning, ladies and gentlemen. On a conspiracy, secret conspiracy, which is about to be made public, the chairman and I have been conferring and he handed me the gavel so that we could have a ceremonial shift in gavel.

Senator Harkin and I, who have traded positions as the powers have flowed, have always talked about it being a seamless change in the gavel. So I want to express my appreciation to Senator Harkin for handing me the gavel and to announce publicly that I'm not going to give it back.

But on a serious level, it doesn't happen too often in the Senate, Tom Harkin and Arlen Specter have worked very closely together for more than two decades, since Senator Harkin was elected in 1984, and I think that has benefited the American people and the health community and the education community and worker safety and labor, where those three departments are under the funding of this subcommittee. In a contentious political climate in Washington, this is we think the way it ought to be operated.

So here comes the seamless transfer, Mr. Chairman.

Senator HARKIN. Well, thank you. Thank you, Arlen, very much. Let me thank my friend and colleague for his kind words, and for 22 years of very close cooperation and a great working relationship.

It has been, I was just counting up, this is the fourth time, Arlen, that this thing has gone back and forth between us, and it has been great working together. Even our staffs, I mean, I think if I'm not mistaken, I think because of the shift and all that kind of stuff and the reallocation and all that, I think some of his staff have just come over to my staff. It's hard to say where one leaves and one takes off, and I think that's the way it ought to be because we're all sort of in the same boat here, trying to do the same job.

I just want to thank you, Senator Specter, for your great leadership in the last—well, there's been so many breaks here—the last

4 years, and then before that 10 years on this committee. It was under your leadership that we were able to double the funding for NIH, more than double it, as a matter of fact. It was under your leadership that we accomplished that, and you did it through two different administrations, one Democrat, one Republican.

It's been under your leadership that we have begun to address a lot of the real issues, health issues confronting the American people, one of which we're going to discuss here this morning. I would say without any hesitation, if there is one person who has really pushed hard on basic medical research, and here I talk about stem cell research and really taking the lead in that and getting the public informed, Arlen Specter has been on the head of that.

So I hope you will all join me in thanking Senator Specter for his great leadership and our continued working relationship on this committee. Thank you, Arlen.

Senator SPECTER. Thank you.

OPENING STATEMENT OF SENATOR TOM HARKIN

Senator HARKIN. I guess, since I've got the gavel, the Subcommittee on Labor, Health and Human Services, and Education, and Related Agencies, Appropriations Subcommittee, will come to order. Again, I want to welcome all of you to this hearing titled "Pandemic Flu: Progress Made and Challenges Ahead."

As you all know, the threat of pandemic flu has not abated. It may have fallen briefly from the headlines, but the problem remains. Bird populations across Asia have been infected by the H5N1 strain of avian influenza. The virus has spread as far as Eastern Europe. Hundreds of people have died.

It may be only a matter of time before this virus mutates and sustained human-to-human transmission occurs. If this virus is able to do this, achieve this, which has been the history of viruses, millions of people may die worldwide, rivaling the Spanish Influenza outbreak of 1918 and 1919. The CDC has estimated that a medium level pandemic could kill over 200,000 Americans and sicken a third of our population.

Now just a little history here. The President's original request to combat the pandemic threat was $7.1 billion in 2005. To date, this committee, again under Senator Specter, appropriated $6.1 billion for pandemic flu preparedness, including $600 million for State and local preparedness. This money has gone to build vaccine capacity, purchase egg-based vaccines, accelerate cell-based vaccine capability, stockpiling antivirals, improving lab capacity at the CDC, and improving surveillance.

In addition, Congress has given HHS new authority to develop the tools we need to respond to mass casualty events. Last year we passed and the President signed into law the Pandemic and All Hazards Preparedness Act that was led by my friend Senator Burr, who led that effort in the authorizing committee, the Health Committee, and I was proud to work with him on that.

Both Congress and the administration are responding to this threat, but our activities raise new questions. Are we investing in the right vaccine technology? Should we invest in other capabilities beyond cell-and egg-based vaccines? How will this new barter, as it's called, within HHS change the way we develop vaccines? Are

we doing all we can to make sure State and local agencies have the ability to respond?

So those are some of the questions that I would pose, and to answer these questions and to bring us up to date we have a very distinguished panel. I thank them all for being here.

PREPARED STATEMENT

Dr. Anthony Fauci, of course, serves as the Director of the National Institute of Allergy and Infectious Diseases at the National Institutes of Health. Dr. Gerald Parker serves as the Principal Deputy Assistant Secretary in the Office of the Assistant Secretary for Preparedness and Response at HHS. Dr. Julie Gerberding has served as the Director of the Centers for Disease Control and Prevention since July 2002. So we are just very grateful for all of your leadership, look forward to your testimony, but before that I would yield to Senator Specter.

[The statement follows:]

PREPARED STATEMENT OF SENATOR TOM HARKIN

Good Morning. I want to welcome you all to this Labor, Health, Human Services, and Education Appropriations Subcommittee hearing entitled: "Pandemic Flu: Progress Made and Challenges Ahead."

As you all know, the threat of pandemic flu has not abated. It may have fallen briefly from the headlines, but the problem remains. Bird populations across Asia have been infected by the H5N1 strain of avian influenza and the virus has spread as far as Eastern Europe. Hundreds of people have died and it may be only a matter of time before the virus mutates and sustained human-to-human transmission occurs. If the virus is able to achieve this, millions of people may die worldwide, rivaling the Spanish Influenza outbreak in 1918–1919. The CDC estimates that a "medium-level pandemic" could kill over 200,000 Americans and sicken one-third of the U.S. population.

The President's original request to combat the pandemic threat was $7.1 billion in 2005. To date, we have appropriated $6.1 billion for pandemic flu preparedness, including $600 million for state and local preparedness. This money has gone to build vaccine capacity, purchase egg based vaccines, accelerate cell-based vaccine capability, stockpile anti-virals, improve lab capacity at the CDC, and improve surveillance. But there is still more to do.

In addition, Congress has given HHS new authority to develop the tools we need to respond to mass casualty events. Last year, we passed, and the President signed into law, the Pandemic and All-Hazards Preparedness Act. My good friend Senator Burr led the effort in the HELP Committee and I was proud to work with him on the legislation. Importantly, part of this bill changed the way the government works with the private sector to develop countermeasures to biological threats, including avian flu.

Both Congress and the administration are responding to this threat. But our activities also raise new questions. Are we investing in the right vaccine technology? Should we invest in other capabilities beyond cell and egg based vaccines? Also—How will the Biomedical Advanced Research and Development Authority within HHS change the way we develop vaccines? In addition, are we doing all we can to make sure State and local governments have the ability to respond?

To answer these questions we have a distinguished panel.

Anthony S. Fauci, M.D. serves as the Director of the National Institute of Allergy and Infectious Disease at the National Institutes of Health. He oversees an extensive research portfolio of basic and applied research to prevent, diagnose, and treat infectious diseases such as HIV/AIDS and other sexually transmitted infections, influenza, tuberculosis, malaria and illness from potential agents of bioterrorism. He received his M.D. degree from Cornell University Medical College in 1966. He then completed an internship and residency at The New York Hospital-Cornell Medical Center.

Dr. Gerald W. Parker serves as the Principal Deputy to the Assistant Secretary, Office of the Assistant Secretary for Preparedness and Response at the Department of Health and Human Services. Prior to joining the Department of Health and Human Services in July 2005, Dr. Parker was at the Department of Homeland Se-

curity from April 2004 to July 2005, and he had 26 years of active U.S. Army service as a researcher. Dr. Parker graduated from Texas A&M University with a Bachelors of Science in Veterinary Medicine and with a degree of Doctor of Veterinary Medicine. He holds a Doctorate in Physiology from Baylor College of Medicine in Houston, Texas and a Masters of Science in Resourcing the National Strategy from the Industrial College of the Armed Forces.

Dr. Julie Gerberding has served as the Director of the Centers for Disease Control and Prevention since July 2002. Prior to taking over CDC, Dr. Gerberding was Acting Deputy Director of the National Center for Infectious Diseases (NCID), where she played a major role in leading CDC's response to the anthrax bioterrorism events of 2001. She earned a B.A. magna cum laude in chemistry and biology and an M.D. at Case Western Reserve University in Cleveland, Ohio. Dr. Gerberding then completed her internship and residency in internal medicine at UCSF, where she also served as Chief Medical Resident before completing her fellowship in Clinical Pharmacology and Infectious Diseases at UCSF. She earned an M.P.H. degree at the University of California, Berkeley in 1990.

Dr. John Treanor is Professor of Medicine, and of Microbiology and Immunology at the University of Rochester. He has done novel research on inhibitors to the influenza virus and on antivirals. He earned his M.D. from the University of Rochester in 1979.

Senator SPECTER. Thank you very much, Mr. Chairman. We have a very distinguished panel here today. When we talk about congressional oversight, when we deal with the National Institutes of Health and the Centers for Disease Control, they don't have to have anybody looking over their shoulders on what they're doing on medical research and protecting public health.

But what the Congress needs to do is to be in close touch with those key health agencies to find out what they need to do their job, and funding is extraordinarily difficult. In fact, that is an understatement. It's close to impossible.

Here we are at the end of January 2007, and we do not have a budget for the Department of Health and Human Services for the period beginning October 1, 2006. That's just totally unacceptable. We're still dealing with a continuing resolution. Under a continuing resolution, what happens is that NIH and CDC lose funds.

Beyond the problem of a continuing resolution, we've had cuts. To cut the National Cancer Institute by $50 million, which was done last year, is really scandalous. In 1970 President Nixon declared war on cancer, and had we prosecuted that war with the same attention that we prosecute other wars, a lot of people who have suffered from cancer might have been spared, including Arlen Specter.

Now we look at the pandemic, and Senator Harkin saw this first last year and came up with a proposal for $8 billion, and he was a pretty good negotiator to ask for $8 billion and come up with $7.1 billion. That's pretty good negotiations, but all the funds haven't been forthcoming.

But when you look at the history of this issue and you look back to 1918, when between 500,000 and 670,000 people died in the United States—we can't be exactly sure because that can't be quantified with precision—and 40 million to 100 million died worldwide, and then the very heavy loss of life in 1957 and 1968, you can see how pandemic flu can spread around the world.

We have to be very vigilant, and the vigilance starts right here with the Department of Health and Human Services and the NIH and the CDC, and Tom Harkin and Arlen Specter. So I'm glad to see this is the first hearing that the recycled chairman has called,

and it couldn't be for a more important subject, so thank you, Mr. Recycled.

Senator HARKIN. That term applies to you, too, you know.

Senator SPECTER. I wear that term proudly and am waiting for the next recycling.

Senator HARKIN. Hopefully it's a long cycle.

I recognize Senator Reed for any opening statement.

Senator REED. Mr. Chairman, thank you and thank Senator Specter. I don't have a statement for the record. I just want to welcome the panelists, and particularly thank Dr. Gerberding for her assistance recently, CDC to Rhode Island. We had what the clinicians say is a Mycoplasma event, and your help was deeply appreciated. Thank you, doctor, and thank you for your hospitality in Atlanta. Thank you.

Senator HARKIN. Thank you, Senator Reed.

Senator Durbin.

Senator DURBIN. Thank you very much, Mr. Chairman. I apologize for just walking in at the last minute, and I'm looking forward to the testimony. I'll waive my opening statement.

Senator HARKIN. Thank you very much.

I was told there's a certain protocol, and I do adhere to protocol sometimes. If we could ask Dr. Treanor, who is a professor of medicine and microbiology and immunology at the University of Rochester Medical Center, who will also be testifying, to come up and take the table, we'll do the administration first and then we'll follow up with Dr. Treanor at the end, but no use your sitting out there someplace, Dr. Treanor. Thanks for being here this morning.

So to kick this all off, and again I'm hopeful that—I've got the clock set for 5 minutes—if you could just give us sort of a summation, a 5-minute summation of your testimony, I would be most appreciative. Your full statements will be made a part of the record in their entirety, and we'll start first of course with Gerald Parker. Dr. Parker.

STATEMENT OF DR. GERALD W. PARKER, D.V.M., Ph.D. PRINCIPAL DEPUTY ASSISTANT SECRETARY, OFFICE OF THE ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Dr. PARKER. Thank you, Mr. Chairman and members of the subcommittee. I am honored to be here today to describe for you how HHS is working to improve the preparedness for a potential influenza pandemic, specifically by pursuing a strategic and comprehensive approach for the development and acquisition of medical countermeasures including vaccines——

Senator HARKIN. I don't think your mike is on.

Dr. PARKER. I'm sorry. Is that better? Okay.

We are working collaboratively, this is very important, because we are working very collaboratively as an enterprise with in the department and with our industrial partners on this medical countermeasures program and the program goals that we have established for an influenza pandemic.

We very much appreciate the support from this subcommittee and Congress during fiscal year 2006 for the emergency supplemental, and I thank you very much for this opportunity today to at least give you a brief overview of the progress that we've made

to date on the medical countermeasures development and acquisition programs and on the whole enterprise, from R&D to advanced development to procurement to distribution and so forth. I will focus my remarks really on the medical countermeasures, to include the vaccines, advanced development, acquisitions, antivirals, and just briefly, diagnostics, and then a conclusion.

Our goals, I think they've been articulated before but there are really two primary goals with the vaccines, and that is to establish a dynamic pre-pandemic vaccine stockpile for 20 million persons and, two, to be able to provide pandemic vaccine to all U.S. citizens within 6 months of a pandemic declaration. As far as antivirals, our two goals are to provide influenza antiviral stockpiles for pandemic treatment for 25 percent of the U.S. population, and to provide influenza antivirals for a strategic containment strategy. Then, finally, diagnostics are to develop point-of-care medical diagnostics.

The Pandemic Influenza Medical Countermeasures Program now includes 25 contracts that have obligated over $3 billion to date. This table illustrates the multipronged approach and diversified portfolio of programs that have been established to help us achieve the implementation program for the medical countermeasures program.

I would now like to take the opportunity to talk in a little bit more detail about some of these programs. First, vaccines are the optimal way to control the spread and associated morbidity and mortality of seasonal epidemics or pandemics. The HHS strategy is to simultaneously stockpile a limited amount of pre-pandemic vaccine, build vaccine manufacturing capacity so that we can quickly produce pandemic vaccine should a pandemic occur, and explore approaches using adjuvants. This approach has utility to help strengthen and integrate both the seasonal and pandemic influenza preparedness needs.

We have aggressively established a vaccine advanced development portfolio that includes 4 projects with 10 contracts and obligations of over $1.3 billion to date. These projects support new influenza vaccine technologies and are precursors to enhancing vaccine manufacturing capacity.

First, cell-based. HHS has awarded more than $1 billion to six manufacturers to accelerate the development and production of new technologies for influenza vaccines within the United States. These contracts provide support for advanced development of cell-based production technologies for seasonal and pre-pandemic influenza vaccines.

Additionally, these contracts are facilitating the modernization and strengthening of the Nation's influenza vaccine production by creating an alternative to producing influenza vaccines in eggs. Notably, these contracts required commitments by each manufacturer to establish U.S.-based manufacturing facilities with a vaccine production capacity of at least 150 million doses within 6 months of a pandemic. Currently, six manufacturers are in clinical studies in the United States to determine the safety and immunogenicity of these cell-based products.

Antigen-sparing. Earlier this month, HHS announced the award of contracts totaling $132 million to three vaccine manufacturers

for the advanced development of H5N1 influenza vaccines using an immune system booster called an adjuvant. In the event of an influenza pandemic, a vaccine that uses an adjuvant could provide a way to extend a limited supply to more people.

Another key feature of these adjuvants is that early studies indicate that they may confer cross-protection properties upon influenza vaccines to afford efficacy against "antigenic drift" variants. That is, an H5N1 vaccine made against the circulating strain in 2006 may offer cross-protection against new strains in the future.

The addition of these adjuvants to candidate vaccines has been shown, in initial European clinical studies, to reduce by 10-to-20 fold the amount of antigen per dose needed to achieve effective individual protection. If these studies are confirmed in larger clinical studies, then these adjuvants may make reaching the goal of United States and global vaccine preparedness faster and more feasible, and help to achieve pandemic vaccine goals number 1 and 2.

Senator HARKIN. Can you start to wrap it up?

Dr. PARKER. Yes, sir. As far as vaccine acquisitions, we are currently in procurement of H5N1. We currently have 1.3 million doses of H5N1 Clade 1 vaccine filled in vials. We have more than 6 million doses of H5N1 Clade 1 vaccine in bulk form, awaiting final instructions for filling. We have approximately 5 million doses of Clade 2 vaccine currently under production.

Then a key part of our strategy is to increase the surge capacity, and we really have two main approaches there. One is to look for retrofitting existing manufacturing facilities, either egg-based or cell-based. We anticipating awarding a contract very soon. Then a real key strategy is a follow-on to the cell-based, and that is looking at actually building manufacturing capacity, and we anticipate going out with an RFP for that in fiscal year 2007.

Then, finally, antiviral drugs. We have two major components there, an advanced development effort, and we just recently awarded a contract for an advanced development; and we are very close, we are on track as far as pursuing our strategy for the procurement both for the Federal and the State subsidized component of the antiviral stockpile.

PREPARED STATEMENT

Then finally I will leave discussion on diagnostics to Dr. Gerberding, and I'd just like to conclude that we have moved out aggressively. We appreciate the support from this subcommittee, but I want to emphasize that it is a total team effort within the department and with our Federal interagency partners in this endeavor. We are taking the concept of working as an enterprise very seriously, again from the research and development all the way to distribution. Thank you for this opportunity to give you this brief summary.

[The statement follows:]

PREPARED STATEMENT OF DR. GERALD W. PARKER

Mr. Chairman and Members of the Subcommittee, I am honored to be here today to describe for you how the Department of Health and Human Services is working to improve preparedness for a potential human influenza pandemic, specifically by pursuing a strategic and comprehensive approach to the development and acquisition of medical countermeasures including vaccines, antivirals, diagnostics, and

through building domestic manufacturing infrastructure for influenza vaccines. We are working cooperatively to leverage resources throughout the Department and with industry to meet the program goals. We recently formalized linkages within HHS through the establishment of the Public Health Emergency Medical Countermeasures Enterprise, led by the leaders of the Office of the Assistant Secretary for Preparedness and Response, the Centers for Disease Control and Prevention, the National Institutes of Health, and the Food and Drug Administration. Thank you for the invitation to testify on this topic which Secretary Mike Leavitt has made a top priority.

On November 1, 2005, the President requested $7.1 billion in emergency funding for the National Strategy for Pandemic Influenza, of which $6.7 billion was designated for HHS. Congress appropriated $3.8 billion in December 2005 as the first installment of the President's request to begin these priority activities, and of this amount, $3.3 billion was provided to HHS. The second appropriation in June 2006 provided HHS with $2.3 billion. We appreciate the action of Congress on these appropriations, as it takes us an essential step forward in becoming the first generation in history to be prepared for a possible pandemic.

The potential for a human influenza pandemic is a current public health concern with an immense potential impact. We know that the influenza virus has the potential to cause a pandemic but we don't know when a pandemic will occur. We don't know how severe a pandemic might be and we don't know which influenza virus will be the one that develops the ability to spark a pandemic. However, we do know that the H5N1 strain of avian flu has spread to more than 50 countries and has led to the deaths of hundreds of millions of birds, and that more than 260 human cases of avian influenza (so called "bird flu") have occurred in 10 countries. More than half of those persons infected have died. This has heightened global concern about the possibility of a human flu pandemic. To date, H5N1 avian influenza has remained primarily an animal disease, but should the virus mutate further and acquire the ability for sustained transmission among humans, a severe influenza pandemic could result that may have grave consequences for global public health. And while a mild pandemic would be primarily a public health problem, the consequences of a severe pandemic on the global economy and on the functioning of society could be enormous.

NATIONAL AND HHS-SPECIFIC PANDEMIC INFLUENZA PLANS

On November 1, 2005, the President announced the National Strategy for Pandemic Influenza, with the three pillars of Preparedness and Communications, Surveillance and Detection, and Response and Containment.

The day after the release of the President's National Strategy for Pandemic Influenza, Secretary Leavitt announced the HHS Pandemic Influenza Plan—a blueprint for all HHS pandemic influenza preparedness and response planning—and released Parts 1 and 2. Part 1, the HHS Strategic Plan, outlines Federal plans and preparation for public health and medical support in the event of a pandemic. It identifies the key roles of HHS and its agencies in a pandemic and provides planning assumptions for federal, state and local governments and public health operations plans. Part 2, Public Health Guidance for State and Local Partners, provides detailed guidance to state and local health departments in 11 key areas.

In May 2006, the National Strategy for Pandemic Influenza Implementation Plan was released. It translated the National Strategy for Pandemic Influenza into more than 300 actions, timelines, and metrics for Federal departments and agencies and set clear expectations for State and local governments and other non-Federal entities. One of the Federal priority actions was to "Accelerate the Development of Medical Countermeasures" and included these efforts:

—Establish stockpiles of vaccine and antiviral medications

—Advance technology and production capacity for influenza vaccine

—Develop rapid diagnostics

Cascading from the National Strategy and National Implementation Plan, one of the key components of the HHS plan called for increasing capacity to produce pandemic influenza antivirals and vaccines, and increasing stockpiles of these countermeasures. Specific strategic goals for pandemic medical countermeasures are displayed in Table 1.

TABLE 1.—HHS PANDEMIC MEDICAL COUNTERMEASURE GOALS

Vaccine Goal #1	To establish and maintain a dynamic pre-pandemic influenza vaccine stockpile sufficient for 20 million persons (at 2 doses/person): H5N1 vaccine stockpiles.
Vaccine Goal #2	To provide pandemic vaccine to all U.S. citizens within 6 months of a pandemic declaration: 600 million doses pandemic vaccine.
Antivirals Goal #1	To provide influenza antiviral drug stockpiles for pandemic treatment of 25 percent of U.S. population: 75 million treatment courses.
Antivirals Goal #2	To provide an influenza antiviral drug stockpile for strategic limited containment at onset of pandemic: 6 million treatment courses
Diagnostics Goal #1	To develop new high throughput laboratory and Point of Care (POC) influenza diagnostics for pandemic virus detection.

The Pandemic Influenza Medical Countermeasure Program now includes 25 contracts obligating over $3 billion. Table 2 illustrates the multi-pronged approach and diversified portfolio of programs that have been established to help us achieve the Implementation Plan's medical countermeasure goals.

TABLE 2.—HHS PANDEMIC INFLUENZA MEDICAL COUNTERMEASURE PROGRAMS

	Vaccines	Antivirals	Diagnostics
Advanced Development	Cell-based Antigen-sparing Next Generation Egg-based Supply	Peramivir	High Throughput. Point of Care. Clinical Lab.
Acquisitions	H5N1 Vaccine Stockpiles	Tamiflu® & Relenza® Federal Stockpiles State Stockpiles	
Infrastructure Building	Retrofit Existing Mfg Facilities Build New Cell-based Mfg Facilities		

I would now like to take this opportunity to provide details about the substantive progress toward meeting our public health emergency preparedness goals in each of these medical countermeasure programs.

VACCINES

Vaccines are the optimal way to control the spread and associated morbidity and mortality of seasonal epidemics or pandemics. Broadly speaking, our approach to developing vaccines for a pandemic may be divided into two categories: those that are developed against strains of animal influenza viruses that have caused isolated infections in human, which may be regarded as "pre-pandemic" vaccines; and those that are developed against strains that have evolved the capacity for sustained and efficient human-to-human transmission ("pandemic" vaccines). Because emergence in human populations necessarily reflects genetic changes within the pandemic virus, pre-pandemic vaccines may be a good or poor match for—and offer greater or lesser protection against—the pandemic strain that ultimately emerges. Thus, the HHS strategy is to simultaneously stockpile a limited amount of pre-pandemic vaccine, build vaccine manufacturing capacity so that we can quickly produce pandemic vaccine should a pandemic occur, and explore approaches utilizing adjuvants to enhance the likelihood that a vaccine administered prior to a pandemic will provide useful protection during a pandemic. Further, this approach will strengthen and integrate both the seasonal and pandemic influenza preparedness needs.

VACCINES—ADVANCED DEVELOPMENT

The Office of the Assistant Secretary for Preparedness and Response (ASPR) supports vaccine advanced development and is currently managing a program that includes 4 projects with 10 contracts and obligations over $1.3 billion (Table 3). These projects support new influenza vaccine technologies and are precursors to enhancing vaccine manufacturing capacity.

TABLE 3.—HHS ADVANCED DEVELOPMENT VACCINE PROJECTS

Projects	Contracts	Awarded	Duration	Goals/Results
Cell-based	6	$1.1 billion	2005–2011	Expand domestic flu vaccine mfg. Capacity to produce 475 M doses pandemic vaccine by 2013.
Antigen-sparing	3	$133 million	2007–2012	Reduce amount of vaccine antigen needed in order to increase the number of doses that can be produced.
Next Generation	([1])	([2])	2007–2012	Diversify flu vaccine mfg. Reduce mfg. time
Egg-based Supply	1	$43 million	2004–2008	Provide year-round egg supply for flu vaccine mfg. Provide clinical study vaccines.

[1] RFP in fiscal year 2007.
[2] To be determined.

CELL-BASED PROJECTS

As part of the President's plan to prepare for a pandemic, HHS awarded in May 2006 more than $1 billion to accelerate development and production of new technologies for influenza vaccines within the United States. These five contracts and an additional contract awarded in 2005 provided support for the advanced development of cell-based production technologies for seasonal and pre-pandemic H5N1 influenza vaccines. Additionally, these contracts facilitated the modernization and strengthening of the Nation's influenza vaccine production by creating an alternative to producing influenza vaccines in eggs. Notably, these contracts required commitments by each manufacturer to establish U.S.-based manufacturing facilities with a vaccine production capacity of at least 150 million doses within 6 months of a pandemic.

Accelerating the development of this vaccine technology and enhancing domestic production capacity are critical enhancements of our public health emergency preparedness efforts. Cell-based vaccine manufacturing—a technology that is used for the manufacturing of many other modern vaccines—holds the potential of a reliable, flexible, and scalable method of producing influenza vaccines.

Using a cell culture approach to produce influenza vaccines offers a number of benefits. Currently licensed influenza vaccines are produced in embryonated hens' eggs in a technique that has changed little in the past 50 years. With increasing demand for seasonal influenza vaccine and with the looming threat of a pandemic, a system that allows surge capacity in an emergency is needed. Vaccine manufacturers utilizing cell-culture technology may be able to bypass the steps needed to adapt the virus strains to grow in eggs, which may save weeks in vaccine production during a pandemic. Since cell-culture technology is used to produce other licensed biologicals, emergency usage of such facilities for pandemic vaccine production is more feasible than with egg-based vaccine manufacturing, which requires highly specialized equipment for egg handling. Further, manufacture of influenza vaccines produced by cell culture also will provide security against risks associated with egg-based production, such as the potential for egg supplies to be unavailable as a result of various poultry-based diseases. Finally, the new cell-based influenza vaccines will provide an option for people who are allergic to eggs and therefore unable to receive the currently licensed vaccines.

Currently, six manufacturers are in Phase 1 clinical studies in the United States to determine the safety and immunogenicity of these cell-based products; however, several of these seasonal influenza vaccine products have already been evaluated clinically in Europe and have been shown to be well-tolerated, immunogenic, and efficacious. H5N1 vaccine products under development in these contracts include inactivated split and whole virion vaccine candidates formulated with adjuvants and live, attenuated virus vaccine candidates. In pursuit of Pandemic Vaccine Goal 2, the impact of these contracts on domestic surge capacity is forecasted to begin by 2009, and will grow through 2013.

ANTIGEN-SPARING PROJECTS

Earlier this month, HHS announced the award of contracts totaling $132.5 million to three vaccine manufacturers for the advanced development of H5N1 influenza vaccines using an immune system booster called an adjuvant, which is a substance that may be added to a vaccine to increase the body's immune response to the vaccine's active ingredient, called an antigen. In the event of an influenza pandemic,

a vaccine that uses adjuvant could optimize utilization of the vaccine stockpile and could provide a way to extend a limited vaccine supply to more people. Another key feature of these adjuvants is that early studies indicate that they may confer cross protection properties upon influenza vaccines to afford efficacy against "antigenic drift" variants—that is, an H5N1 vaccine made against the circulating strain in 2006 may offer cross protection against new H5N1 virus strains emerging in future years.

The contracts provide support for advanced development of antigen-sparing pandemic vaccine with adjuvants through U.S. clinical trials towards U.S-licensure. Further, these contracts facilitate the establishment of manufacturing capabilities for these adjuvants and development of delivery devices, including adjuvant containing patches which could similarly extend a limited vaccine supply.

Under the contracts, each company will build up to a capacity to produce, within 6 months after the onset of an influenza pandemic, either 150 million doses of an adjuvant-based pandemic influenza vaccine or enough adjuvant to be stockpiled for 150 million doses of a pandemic influenza vaccine. In addition to supporting the development of each company's antigen-sparing vaccine candidate, the contracts also require each company to provide its proprietary adjuvant for U.S. Government-sponsored, independent evaluation with influenza vaccines from other manufacturers.

Initial clinical studies conducted by NIH on antigen-alone H5N1 vaccine candidates in humans have shown that two 90-microgram doses of the vaccine are required to stimulate a level of immune response that researchers anticipate would provide protection for an individual against the H5N1 strains that have been spreading among birds in Asia. However, the addition of adjuvant to these candidate vaccines has been shown, in initial European clinical studies, to reduce by 10-to-20-fold the amount of antigen per dose needed to achieve effective individual protection. Phase 1 and 2 clinical studies for safety, immunogenicity, and cross protection are planned in 2007 for the H5N1 vaccine products with the each of the three new adjuvants. If these results are confirmed in larger clinical studies, then these adjuvants may make reaching the goal of United States and global pandemic vaccine preparedness faster and more feasible, and help to achieve Pandemic Vaccine Goals 1 and 2.

EGG-BASED SUPPLY

To be able to manufacture flu vaccines in the event of a pandemic flu outbreak or future vaccine shortages, HHS awarded a contract in November 2004 for $43 million to develop and implement an egg supply plan for transition to a secure, year-round egg supply, stockpile other vaccine manufacturing supplies, such as vials, caps, and stoppers, and to develop and manufacture pandemic vaccine candidates for clinical investigation. In April 2005 a secure year-round egg supply for domestic influenza vaccine manufacturing was realized, and two pandemic vaccine candidates—H5N1 clade 2 and H7N7—have been produced for NIH clinical investigations under this contract.

Vaccines—Acquisitions

ASPR currently has a vaccine acquisition program that includes four projects with six contracts and obligations over $500 million to procure pre-pandemic vaccine (Table 4).

TABLE 4.—HHS H5N1 VACCINE ACQUISITION PROJECTS

[Dollars in millions]

Projects	Contracts	Award	Duration	Goals/Results
H5N1 Vaccine Clade 1—2004	1	$21	2004–2008	Provide 0.47 million doses @ 90 μg/dose
H5N1 Vaccine Clade 1—2005	2	243	2005–2008	Provide 8.0 M doses @ 90 μg/dose
H5N1 Vaccine Clade 2—2006	3	241	2006–2008	Provide 4.9 million doses @ 90 μg/dose
H5N1 Vaccine 2007	([1])	([1])	2007–2009	Provide doses for pre-pandemic stockpile (H5N1)

[1] To be determined.

Manufacturing these pre-pandemic vaccines not only provides the industry experience in producing novel influenza vaccine candidates at a commercial scale, but also provides a foundation for pre-pandemic vaccine stockpiles. In the early stages of a severe pandemic, and before a well-matched vaccine is available, pre-pandemic vaccines may be used in selected populations to mitigate disease, support essential operations, and maintain social and economic systems.

Currently, 1.3 million doses of H5N1 Clade 1 vaccine (90 μg/dose) have been filled in vials. More than 6 million doses (90 μg/dose) of H5N1 Clade 1 vaccine remain in bulk form and await instructions for formulation into final vaccine vials. Additionally, approximately 5 million doses of H5N1 Clade 2 vaccine are currently under production.

VACCINES—INFRASTRUCTURE BUILDING

In order to achieve pandemic preparedness, the influenza vaccine surge capacity needs to be expanded. Expansion of commercial scale egg- or cell-based production could be accomplished by renovation of existing domestic manufacturing facilities already licensed for approved biologicals. Furthermore, pandemic vaccine surge capacity required extension of the time dedicated to its production, as H5N1 vaccine stockpile manufacturing was limited to the 3 months each year when influenza manufacturers are not producing seasonal flu vaccine. Therefore, in July 2006, HHS issued a solicitation for proposals to retrofit or remodel these existing domestic manufacturing facilities and establish warm-base capabilities for the emergency production of pandemic vaccine. HHS plans to award these contracts in February 2007 (Table 5).. These contracts will not only increase domestic pandemic influenza vaccine capacity, but will also allow year-round production of pre-pandemic stockpiles.

To further capitalize on the promise of cell-based influenza vaccines, HHS plans to issue an RFP later this year to assist in the establishment of new U.S.-based vaccine manufacturing facilities for the production of cell-based seasonal and pandemic influenza vaccines (Table 5), helping us achieve Pandemic Vaccine Goal 1.

TABLE 5.—HHS INFLUENZA VACCINE MANUFACTURING INFRASTRUCTURE BUILDING PROJECTS

Projects	Contracts	Award	Duration	Goals/Results
Retrofit existing manufacturing facilities.	Active RFP; contract awards expected Feb. 2007.	([1])	2007–2013	Increase domestic flu vaccine capacity to produce 125 M doses of egg-based pandemic flu vaccine.
Build new cell-based vaccine facilities.	RFP expected in fiscal year 2007.	([1])	2008–2013	Build domestic cell-based flu vaccine mfg. capacity to support pandemic needs.

[1] To be determined.

ANTIVIRAL DRUGS

Antivirals are principally used to treat influenza infections. Under certain circumstances, antivirals may also reduce transmission of the influenza virus or even prevent infection. Two antiviral drugs were effective against the H5N1 virus in laboratory testing. In the event of a pandemic, antiviral drugs may be a key line of defense before a well-matched pandemic vaccine is available.

HHS funding was therefore allocated to acquire antiviral drugs. Currently two drugs, oseltamivir (Tamiflu®) and zanamivir (Relenza®) may provide clinical benefit against most H5N1 virus strains currently circulating in Asia; however, several cases of drug-resistant H5N1 viruses in humans have been identified. Accordingly HHS is stimulating the development of new and more promising influenza antivirals and establishing antiviral drug stockpiles to achieve antiviral goals #1 and #2.

ANTIVIRAL DRUGS—ADVANCED DEVELOPMENT

ASPR has an antiviral advanced development program that earlier this month awarded a $102 million contract for the development of a new influenza antiviral—Peramivir, which is a member of the neuraminidase inhibitor class of influenza antiviral drugs (Table 6). The drug resistant profile for Peramivir is dissimilar to those of the licensed antiviral drugs. While the other antiviral drugs in this class are either taken orally (oseltamivir/Tamiflu®) or by an inhaler (zanamivir/Relenza®), peramivir is being studied as a drug that can be administered parenterally, that is through intravenous or intramuscular injection.

TABLE 6.—HHS INFLUENZA ANTIVIRAL DRUG ADVANCED DEVELOPMENT PROJECT

[Dollars in millions]

Project	Contracts	Award	Duration	Goals/Results
New influenza antiviral drugs ..	1	$102	2007–2011	Expand and diversify flu antivirals. Develop peramivir for IM/IV administration.

Funding in this contract over the next 4 years will support manufacturing of clinical investigational and consistency lots; Phase 2 and 3 clinical studies to evaluate safety and efficacy in support of product approval in the United States; manufacturing process validation; and other product approval requirements.

ANTIVIRAL DRUGS—FEDERAL AND STATE ACQUISITIONS

Another key goal in the HHS Pandemic Influenza Plan is to ensure the availability of antiviral treatment courses for 25 percent of the population, or 75 million individuals. By fiscal year 2008, the Federal government will complete the 20 million course antiviral stockpile purchase to maintain the function of the health care system and protect first responders, and stockpile an additional 24 million treatment courses for treatment of pandemic influenza, for a total of 44 million treatment courses. In addition, the Federal government plans to stockpile 6 million treatment courses to attempt to contain no more than two local outbreaks at the outset of a pandemic in the U.S. To date, HHS has ordered more than 36 million courses of influenza antivirals for which 26 million courses have been delivered to the Strategic National Stockpile for pro rata distribution to States during a pandemic (Table 7). A small portion of the Federal stockpile has been deployed to eastern Asia to help contain a potential outbreak.

TABLE 7.—HHS INFLUENZA ANTIVIRAL DRUG STOCKPILE PROJECTS

Projects	Contracts	Award	Duration	Goals/Results
Federal pan flu antivirals stockpiles.	2	$587 million	2004–2008	Build federal stockpile of pan flu antivirals for containment & treatment (50 million treatment courses total).
State pan flu antivirals stockpiles.	2	$170 million budget	2006–2008	Subsidize purchase of pan flu antivirals by States and other entities to build stockpile of 31 million treatment courses.

Additionally, the Implementation Plan calls for States to purchase 31 million antiviral treatment courses, for which the Federal government subsidizes at 25 percent of the cost ($170 million total).

In summer 2006, HHS announced two-year contract awards totaling $166 million that provided discounted prices for all 50 States, the District of Columbia, five U.S. territories, and the three Freely Associated States of the Pacific to purchase influenza antiviral drugs for State pandemic stockpiles. At the time, Secretary Leavitt commented, "Our ultimate goal is to stockpile sufficient quantities of antiviral drugs to treat 25 percent of the U.S. population. Helping the states develop their own medical stockpiles will facilitate quicker distribution of antiviral drugs in the event of a pandemic influenza outbreak."

To date 43 States have ordered 11 million treatment courses and are committed to purchasing 30.6 million treatment courses by 2008. A complete table of projected antiviral purchases and subsidized allocations for all jurisdictions is posted online at http://www.pandemicflu.gov/state/antivirals.html.

DIAGNOSTICS

Funding has been designated for the advanced development of rapid detection tests for avian influenza in humans. CDC, with the assistance of ASPR, currently has an advanced development program for point of care diagnostics that includes four contracts and obligations over $11 million (Table 8).

TABLE 8.—HHS PANDEMIC RAPID DIAGNOSTICS DEVELOPMENT PROJECTS

Projects	Contracts	Award	Duration	Goals/Results
POC flu diagnostics	4	$11.4 million for year 1.	2006–2007	Facilitate development of point of care diagnostics towards U.S.-approval for detection of pandemic flu viruses.

In December 2006, HHS announced $11.4 million in new contracts to four companies working to develop new point of care diagnostic tests that doctors and field epidemiologists could eventually use to quickly and accurately test patients for avian influenza H5N1, other emerging influenza viruses, as well as more common influenza viruses. The tests could provide public health experts worldwide with critical information on the influenza viruses circulating and help monitor for viruses that could cause a global influenza pandemic.

During the next year, the four companies will work to create tests that would detect seasonal human influenza viruses and differentiate within 30 minutes influenza A H5N1 from seasonal human influenza viruses. These contracts, in support of diagnostics goal #1, will stimulate development of promising technology that could help doctors treat their patients faster and help public health authorities track influenza viruses that could spur a pandemic, and may be used at points of entry for screening. In addition to these contracts, CDC will provide funding for a repository of influenza reagents and other materials to aid with the advanced development of these point-of-care diagnostics.

NON-PHARMACEUTICAL MEDICAL SUPPLIES AND RESPONSE CAPACITY

HHS is expanding medical infrastructure and response capacity during an influenza pandemic by stockpiling non-pharmaceutical medical supplies for distribution to States in the event of a pandemic. HHS has purchased over 155 million masks to reduce the spread of disease. In addition, HHS has obligated $100 million for the purchase of ventilators, intravenous antibiotics, syringes and needles. Of the $170 million allocated, over $156 million has been obligated for medical supplies.

HHS has also directed funding to increase State and local capacity, enhance international surveillance, expand clinical research capacity Southeast Asia, and implement rapid outbreak response in currently affected countries. HHS has also allocated funds for risk communication strategies and other domestic preparedness activities. Lastly, ASPR has provided grants in 2006 for $11 million to Vietnam and the World Health Organization for in-country development of H5N1 vaccine candidates.

CONCLUSION

I hope my testimony today has provided you a summary of the tremendous progress that has been made by the Department of Health and Human Services' enterprise and its industrial partners to develop and acquire medical countermeasures to improve our preparedness for an influenza pandemic. As described:

—HHS initiated and/or awarded contracts for all of the first phase medical countermeasure development and acquisition programs within one year of the initial appropriation in December 2005,

—HHS is managing a robust and comprehensive portfolio with over two dozen contracts, and

—HHS is initiating phase 2 initiatives for vaccine infrastructure building and managing vaccine and antiviral stockpiles.

Although much has been accomplished, continued vigilance and preparation are needed for us to be ready for Influenza—seasonal epidemics and Pandemics.

Thank you for the opportunity to share this information with you. I am happy to answer any questions.

Senator HARKIN. Thank you, Dr. Parker.

Dr. Gerberding.

STATEMENT OF DR. JULIE L. GERBERDING, M.D., DIRECTOR, CENTERS FOR DISEASE CONTROL AND PREVENTION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Dr. GERBERDING. Good morning. I'm very pleased to have an opportunity to testify before the subcommittee, and I just personally thank both of you, Senator Specter and Senator Harkin, for your

ongoing interest and the detailed effort that you make to understand the pandemic and why that's important. I really appreciate being here.

I am going to do two things. First, I would just like to give a brief situation report on the status of the H5N1 avian problem that we're experiencing, and then summarize for you the pandemic preparedness efforts that CDC is leading on behalf of Secretary Leavitt and the department.

So I have a graph that I think even from a distance you can see has a lot more color on it than it did a year ago. These are all the countries that have had poultry outbreaks. The orange countries are countries where the problem has been primarily in domestic poultry. The yellow countries have not had domestic outbreaks but have had cases detected in wild birds.

You can see that this really involves many continents, and what we've learned from watching this, number one, is that there is seasonality to the outbreaks. We're in high season right now in Asia. So we see a cyclical pattern. We also know that this is very lethal for birds. Broad species die.

Most importantly, we know this virus is not just moving geographically but it's moving biologically. It's mutating and evolving. We now have two main families of virus, and the second family has split off into three sub-families. So we're watching the inevitable evolution of the H5N1 virus over time, and that of course makes it more challenging for us to develop seed viruses for vaccines, and for Dr. Fauci and others to stay on top of the vaccine development.

On the next graphic I have a map that sadly has many red areas. These are the countries that have had human cases where the virus has spilled over, and you can see again this map is much redder than it was a year ago because more countries, more cases.

What we've learned from this experience is that this remains a very unusual event, for people to pick up the virus. Most of this has occurred from bird to human, but we have had small clusters of human-to-human transmission that have been well documented, and sadly, very high fatality rates here. We're still seeing, of the 269 cases, the mortality rate is much greater than 50 percent.

Just in the first 24 days of January we've had seven new cases in India and Egypt. Six of those seven patients died from H5N1 influenza.

On the next graphic I'm showing geographically where CDC along with other Federal partners is investing effort to try to stay on top of the global situation. The green countries are basically places where CDC has provided resources to the ministries of health or indirectly through other cooperative agreements. All of the little dots on this map are places where CDC either has people or where we have supported the training and development of in-country availability along with our collaborators in USAID.

The good news is, this is a much greener map than it was the last time we were here, but the problem remains. There are still countries that aren't involved in the surveillance, and we still have some black boxes where we just don't get information about evolving health situations, including pandemic.

On the next graphic I have just summarized for you some of the highlights of the progress that we have made in the last year.

When we talk about pandemic preparedness, we are not talking about just H5N1. We are talking about any virus that has the potential to move rapidly from human to human and cause deadly outbreaks.

We need four things to be prepared. We need products, and Dr. Parker and Dr. Fauci will talk more specifically about the vaccine and the antivirals, but we need other products like diagnostic tests. You can see that we're on our way now to develop a rapid diagnostic test through some cooperative agreements and contracts.

We also need plans. CDC has developed a flu operation plan to carry out the Secretary's strategy. We have about 1,000 tasks in that plan, and we have more than 150 people who are working their hearts out, trying to make sure that we accelerate our preparedness not just at CDC but throughout the State and local health departments, the business community, the educational community, and so on and so forth.

So that's plans and products. We also need people, and we have got to invest in the scientists and the preparedness experts at every element of the preparedness network if we want to be successful. CDC is recruiting and developing a much broader cadre of expertise in this area, thanks to the support that we have gotten so far from the supplemental.

The fourth thing we need is practice, and what you're going to see in the next year is a great deal of practice of all of this planning that has gone on in the States and at CDC. You'll be seeing not just tabletops but what we call "crawl walk run" exercise regimens where we gradually scale up our ability to act out our responses in the pandemic and to understand what we need to continue to improve. That is a requirement. That is part of what we're using the resources that Congress has appropriated to the States to accomplish this year, and we think this ultimately is the best way to end up the kind of preparedness we need.

PREPARED STATEMENT

So people, plans, products, and practice is really what we're doing with the investment that you have made in us, and we're very grateful for it.

Senator HARKIN. Thank you very much, Dr. Gerberding.

[The statement follows:]

PREPARED STATEMENT OF DR. JULIE L. GERBERDING

Mr. Chairman and members of the subcommittee: I am pleased to be here today to provide an update on cross-cutting preparations the Centers for Disease Control and Prevention (CDC) and our many partners, collaborators, and other organizations are undertaking for the next influenza pandemic. Secretary Michael O. Leavitt, Secretary of the Department of Health and Human Services (HHS), is strongly committed to preparing for a pandemic. An influenza pandemic would have a profound impact on almost every sector of society, both in the United States and globally. I would like to emphasize the importance of this consolidated approach not only within the realm of public health but across all sectors of society in readiness for the next influenza pandemic. CDC is committed to improving the health of our Nation and the world. Our longstanding emphasis on cooperative action has allowed the public health community to accomplish a great deal since I testified before the Subcommittee last January, and much more needs to be done. I will focus my testimony today on three areas: ongoing domestic and international surveillance, other preparedness initiatives in 2006, and examples of CDC actions planned for 2007 and

beyond. I will also describe the agency's progress towards the President's National Strategy for Pandemic Influenza.

Before continuing my testimony, I would like to thank this subcommittee and the Congress for providing Fiscal Year 2006 Emergency Supplemental funding for pandemic preparedness.

CDC recognizes the continuing threat of avian influenza A/H5N1 as well as other influenza strains that could evolve into a pandemic, and we are committed to take steps necessary for effective preparedness and response. Work clearly must continue to ensure sustained actions that will minimize the morbidity, mortality, economic burden, and social disruption that an influenza pandemic could cause. To put this imperative into perspective, I'd like to share a few comparisons between 2005 and today.

In January 2005, 10 countries that had reported detection of highly pathogenic avian influenza A (H5N1) viruses in wild birds or domestic poultry to World Organization for Animal Health (OIE) (including both China and the Hong Kong Special Administrative Region of China). By January 22, 2007, 56 countries had reported H5N1 in birds (including both China and the Hong Kong Special Administrative Region of China). In January 2005, the World Health Organization (WHO) confirmed 47 human cases with 34 fatalities in two countries. As of January 22, 2007, WHO had confirmed 269 human cases with 163 fatalities in 10 countries.

ONGOING INTERNATIONAL AND DOMESTIC SURVEILLANCE

One of CDC's most important roles in protecting the nation's health is to provide an ongoing assessment of the threat of an influenza pandemic. We collect and disseminate surveillance information for influenza strains circulating throughout the world, including those with a high possibility of evolving into an influenza pandemic. As one of four World Health Organization Global Collaborating Centers for Influenza, CDC is responsible for detecting and reporting predominant influenza strains and coordinating development of annual influenza vaccines for the Northern and Southern Hemispheres.

Our agency is especially focused on monitoring changes in the avian influenza A/H5N1 virus. We are carefully monitoring changes in the H5N1 virus that might allow it to evolve into a strain that could result in a pandemic. Our work in this area is highly collaborative, involving global and regional non-governmental organizations, ministries of health in countries across the world, CDC offices in selected countries, and other United States Government agencies such as Naval Medical Research Units (NAMRU). This extensive surveillance network has made it possible for CDC to closely track the geographic spread of the H5N1 viruses in 2006 and to identify and analyze several subtle changes in the virus. Fortunately, at present, these changes do not appear to have increased the virus' capability for efficient human-to-human transmission. CDC also has been able to identify changes in the composition of H5N1 virus samples that could affect its susceptibility to antiviral medications. A recent example appeared in an H5N1 virus sample from Egypt, initially indicating a change in susceptibility to oseltamivir, better known as Tamiflu™. As WHO has stated, at this time there is no indication that oseltamivir resistance is widespread in Egypt or elsewhere.

Influenza surveillance within the United States is closely linked with seasonal influenza activities. The established domestic surveillance network provides a solid foundation on which CDC and our partners are building the real-time human surveillance that will be vital when an influenza pandemic appears in the United States. We also are working closely with agencies such as the U.S. Geological Survey and the United States Department of Agriculture (USDA) to maintain integrated surveillance of animals infected by avian influenza strains. CDC is cooperating with public and private organizations to monitor migratory wild birds that carry numerous strains of avian influenza. We have strengthened agreements with our neighbors in Canada and Mexico to identify highly pathogenic H5N1 and other potential pandemic strains quickly.

International and domestic surveillance is vital if the United States is to contain viruses that cause influenza pandemics and slow the spread of infection to allow the most time possible for development and dissemination of a pandemic vaccine. If an influenza pandemic expands in the United States, CDC's surveillance efforts will shift focus to supplying the necessary data to track the extent and severity of infection and inform response and recovery efforts.

OTHER PREPAREDNESS INITIATIVES IN 2006

CDC's preparedness initiatives can be grouped under the agency's Health Preparedness Goals. Many of the agency's accomplishments in 2006 bridge these goals,

including the completion and implementation of a comprehensive Pandemic Influenza Operations Plan, an examination by nationally recognized ethicists of ethical issues in the decisions that must be made to achieve preparedness for an influenza pandemic, and the implementation of a cross-cutting Pandemic Influenza Task Force that is focusing on CDC's responsibilities related to the President's Pandemic Influenza National Response Plan.

PREVENTION

In 2006, CDC completed several important preparedness actions related to prevention, in cooperation with parts of the HHS and other organizations.

—CDC played a lead role in most State Influenza Summits coordinated by HHS and has continued follow-up with the States.

—CDC has prepared and disseminated guidance, recommendations and initial funding to the 62 States, localities, territories, and tribal nations that are receiving HHS funding for pandemic influenza preparedness. This guidance included templates for operational drills of influenza immunization clinics and table-top exercises for community-based school-closing decision processes as well a model contract for engaging pertinent private-sector entities in receipt, storage and emergency intra-state distribution of antiviral drugs when an influenza pandemic seems imminent.

—To strengthen seasonal vaccination and prepare a foundation for promotion and distribution of a pandemic influenza vaccine upon availability, CDC held two National Vaccine Summits with partners in 2006 and conducted the first National Influenza Vaccination Week.

—CDC completed its Pandemic Influenza Operations Plan in 2006 and began implementing the plan. As part of this initiative, the agency has begun a systematic series of preparedness exercises.

—CDC and other WHO Global Collaborating Reference Laboratories isolated and characterized strains of avian influenza and with this information recommended representative strains for use in avian influenza vaccines.

—CDC laboratories employed reverse genetics methods to rapidly develop safer strains of newly identified avian influenza viruses for use in vaccine production.

—CDC's 2006 research on the deadly 1918 pandemic influenza increased understanding about the challenges in preventing or minimizing the impact of pandemics.

—As part of United States global cooperation, CDC in collaboration with other parts of HHS, had worked with other agencies to pre-position antiviral regimens overseas to support international containment efforts. This activity is closely coordinated with WHO.

DETECTION AND REPORTING

In 2006, CDC made considerable progress in its detection and reporting goals related to pandemic influenza preparedness.

—CDC awarded four contracts to biotechnology companies to develop easy to use rapid diagnostic tests for detecting avian influenza. These tests can diagnose influenza within 30 minutes and will be used at the point of care such as in doctor's offices, in emergency rooms, or at ports of entry.

—Research accomplishments ranged from development, production and dissemination of new rapid diagnostic tests to development of tests to distinguish H5 viruses from other strains, which now are being used by 113 certified laboratories in the Laboratory Response Network (LRN). These labs have reagents on hand to perform the H5N1 test (assay). Of these, 107 are domestic labs and six are international labs. CDC also conducted extensive research on viral samples to identify changes in the structure of H5N1 subtypes that might indicate greater ability for person-to-person transmission or increased severity of infection.

—To help ensure the prompt identification and containment of people infected by H5N1 and other viruses that could result in an influenza pandemic, CDC and the Council for State and Territorial Epidemiologists (CSTE) continued our cooperative work to make all laboratory-confirmed influenza hospitalizations notifiable. In addition, CSTE recently has recommended that infection with novel influenza viruses be nationally reportable.

TIMELINESS AND ACCURACY OF COMMUNICATIONS

Risk communication planning is critical to pandemic influenza preparedness and response. HHS and CDC are committed to the scientifically validated tenets of outbreak risk communication: comprehensive information shared across diverse audi-

ences, information tailored according to need, and information that is consistent, frank, transparent, and timely.

—CDC developed a comprehensive pandemic influenza risk communication plan based on its nationally recognized risk communications training program. This plan is included in the agency's Pandemic Influenza Operations Plan and will be modified as needed based in part on scheduled pandemic influenza exercises.

—In 2006, CDC developed preparedness checklists and other practical guidance for targeted groups, including the business community and healthcare facilities.

—CDC has contributed substantial information to the national pandemic preparedness web site, www.pandemicflu.gov, including information, education, or guidance documents.

—The agency also enhanced its speaker's bureau and hotline to accommodate increased requests for presentations about pandemic influenza preparedness. Since February 2006, the CDC Speaker's Bureau has recorded as accepted more than 115 presentations to groups in the United States and internationally on pandemic influenza.

INVESTIGATION AND CONTROL

CDC's investigation and control efforts focus on decreasing the time needed to identify causes, risk factors, and appropriate interventions for those affected by the threat of pandemic influenza. These efforts include activities that support rapid outbreak response and purchasing and stockpiling of antiviral medications and other materiel.

—Rapid response to international outbreaks has been a part of CDC's mandate for decades, but recently published work suggesting challenges involved in slowing or containing an influenza pandemic clarifies the importance of such response capabilities. For optimal response, an emerging influenza pandemic outbreak anywhere in the world must be recognized within 1 to 2 weeks and investigated and virologically confirmed within days. An unprecedented and well-coordinated containment effort must be launched in stages in response to preplanned trigger points, including deployment of dozens of trained teams, public health messages, social isolation measures, movement restriction considerations, treatment of patients, and tracing and prophylaxis of contacts. During an international training meeting in Bangkok, Thailand in July 2006, CDC unveiled a new, one-week standard curriculum to train local rapid response teams throughout the world. This program was developed in collaboration with the University of North Carolina School of Public Health and provides essential response skills to Rapid Response Teams composed of medical doctors, epidemiologists, veterinarians, nurses, laboratorians, communications specialists and other health responders.

—In 2006, CDC awarded a total of 21 new Cooperative Agreements supporting avian and pandemic influenza detection and response to all six WHO regional offices and countries throughout the world, bringing the total number of grantees supported by CDC to 47.

—The agency deployed investigative teams to many countries that experienced H5N1 outbreaks, including Indonesia, Turkey, Azerbaijan, Djibouti, Nigeria, and Sudan. These teams often contributed to investigations coordinated by WHO or requested specifically by ministries of health. Other teams were part of multi-agency U.S. Government initiatives. For example, in Azerbaijan, CDC subject matter experts visited as part of the Department of State visit and advised on outbreak control. In addition, CDC staff that are stationed in China, Thailand, Cambodia, and Laos have participated in investigations.

—CDC also collaborated with USDA and numerous other Federal partners to develop a playbook that systematically addresses scenarios and roles for responding to the introduction of H5N1 and other avian influenza viruses by wild birds and domestic animals.

—CDC developed a comprehensive Global Disease Detection (GDD) strategy and in 2006 expanded its international surveillance, diagnosis, and epidemic investigations, which are integrated with WHO and other international partners.

—In 2006, in collaboration with WHO and other partners, CDC enhanced sharing of influenza virus genetic sequences as part of an international effort to increase information for research into pandemic influenza.

—Last year, CDC significantly increased supplies in the Strategic National Stockpile, including antiviral medications, personal protective equipment, and other vital material, which will be used in the event of a pandemic.

—The agency has worked extensively with sister-agencies, partners, and public groups to develop health guidance specifically for pandemic influenza. This in-

cludes development of technical guidance for health-care workers on the use of personal protective equipment.

RESPONSE AND RECOVERY

The U.S. healthcare system will be severely stressed by an influenza pandemic. In addition to critical preparation needed to respond successfully to the acute medical care needs of the population, the healthcare system will also need to resume normal services as rapidly as possible. Among its actions, the Pandemic Influenza Task Force in 2006 enhanced planning for recovery of vital public health services.

—CDC has developed, with input from State and local health departments, healthcare partners, and other Federal agencies, guidance to assist healthcare facilities in developing and implementing plans to respond to an influenza pandemic, including guidance on the use of appropriate infection control measures to minimize transmission during patient care.

—Participation in tabletop exercises during the past year has helped facilities identify gaps and improve their readiness to respond and recover after a pandemic, as an integrated part of the overall planning and response efforts of their local and State health departments.

CDC ACTIONS FOR 2007 AND BEYOND FOR CONTINUING

The following highlights some of the actions in which CDC now is engaged.

1. CDC will continue ongoing activities with State, local, territorial, and tribal nation grantees. These activities will include review and monitoring of preparedness efforts, technical assistance and guidance on exercise programs, analysis of potential gaps in preparedness plans, and promotion of best practices among grantees.

2. A large CDC internal pandemic influenza preparedness exercise is scheduled for January 31–February 1, 2007. Additional exercises that will include other agencies and groups will be scheduled as the year progresses.

3. CDC, building on its successful 2006 National Influenza Vaccination Week, and in collaboration with HHS and others, will make this an annual event for promoting the importance of influenza vaccination.

4. CDC, in partnership with the Council for State and Territorial Epidemiologists (CSTE) is overseeing adaptation of the international Rapid Response curricula for use domestically in each state. CD–ROM and web-based versions of the trainings are in development for use by field staff and other partners as a self-study curriculum.

5. CDC is working with HHS to develop and implement a National Education Campaign for Pandemic Preparedness, which will include a focus on vulnerable populations.

6. CDC will provide training and support to other countries to improve avian and pandemic influenza preparedness and response.

7. CDC laboratories will rapidly characterize avian and other influenza viruses to monitor for emergence of potential pandemic strains and to develop strains for use in vaccine production.

8. CDC will complete the collaborative guidance document on the use of personal protective equipment by the public. CDC also will publish preliminary guidance on community mitigation strategies to educate the public, private sector, and our state and local partners about use of non-pharmaceutical interventions, which will be especially important in the initial months of an influenza pandemic. This guidance will be refined and updated as necessary.

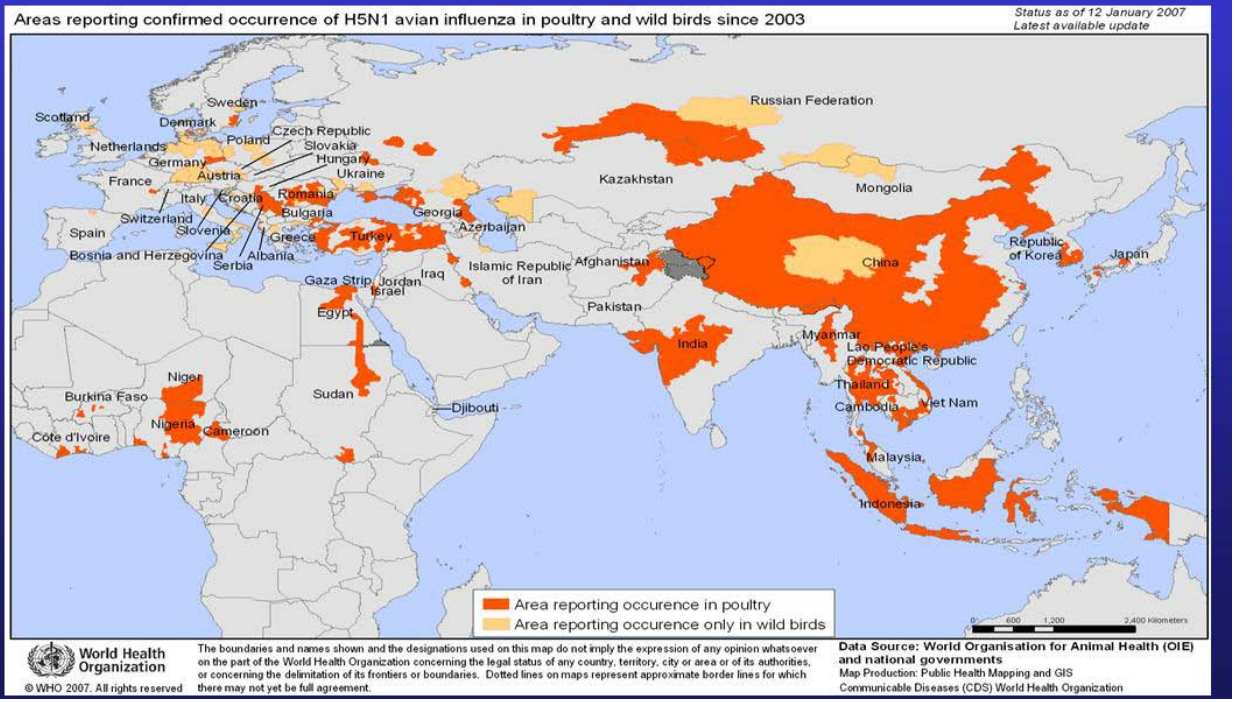
9. CDC continues toward the goal of developing the coordinated quarantine and screening capacity. This will include efforts in a range of areas, including continued strengthening of quarantine stations at major ports of entry, initiatives with border security as part of our discussions with public health counterparts in Mexico and Canada, and addressing possible legal and ethical questions regarding isolation and quarantine measures in communities to impede the spread of viral infection.

CONCLUSION

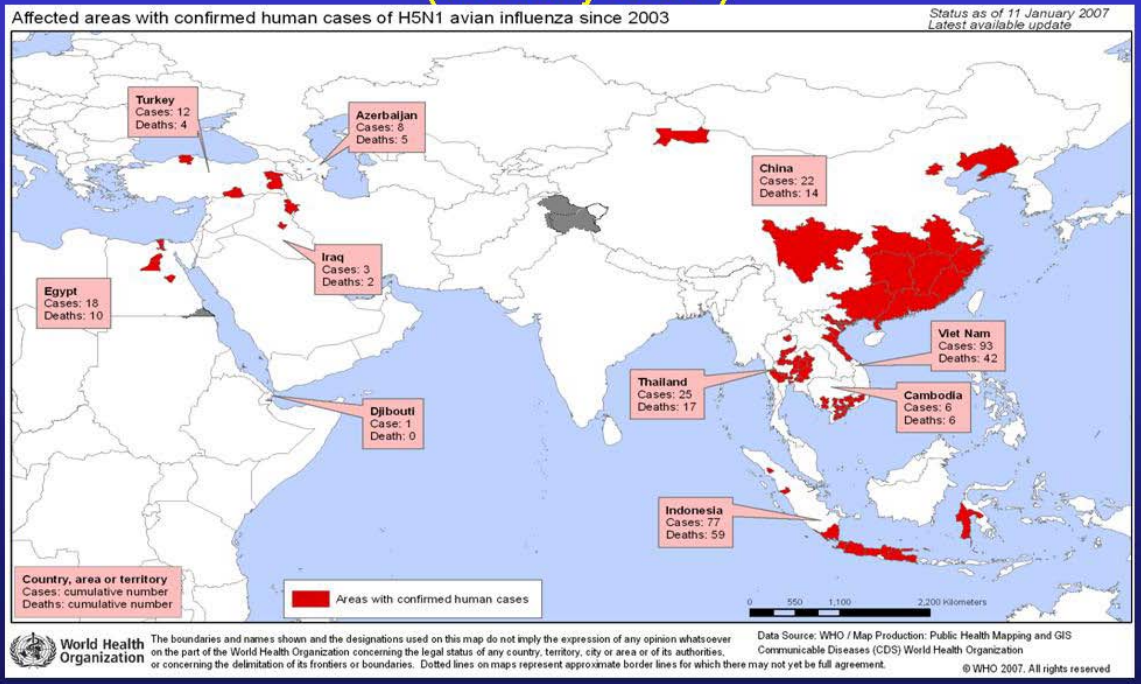
Although CDC and its many partners accomplished much for pandemic influenza preparedness and response during 2006, from a public health standpoint much more preparation is needed. CDC greatly appreciates the support of this Subcommittee and others in 2006 and looks forward to working with you to sustain these accomplishments.

Thank you for the opportunity to share this information with you. I am happy to answer any questions.

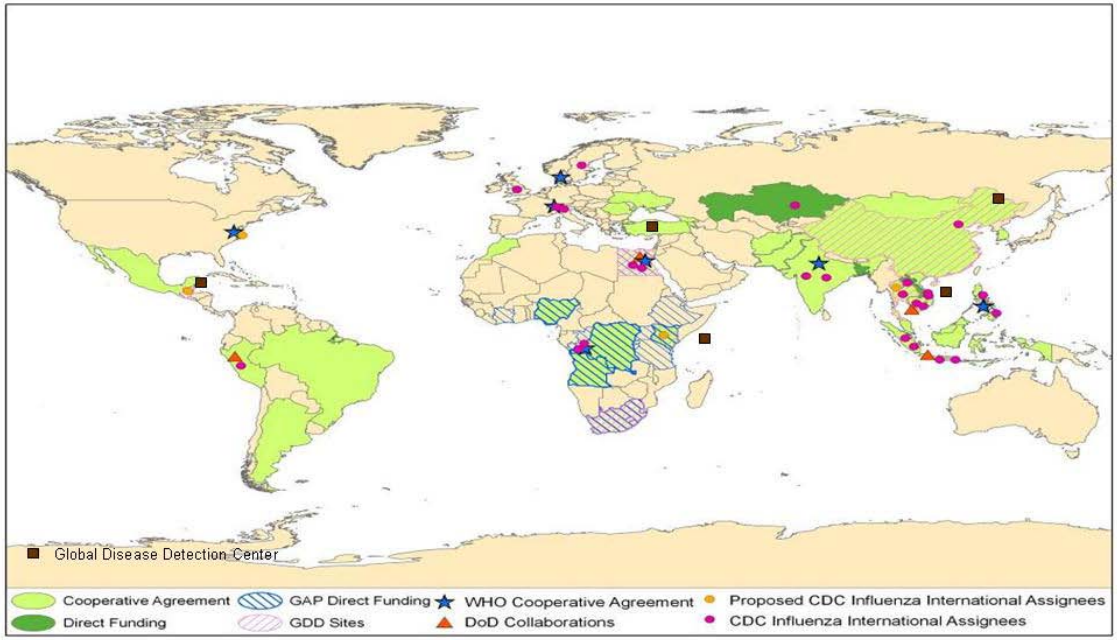
Avian H5N1 Influenza: Wild Bird/Poultry Status (January 2007)



Avian H5N1 Influenza: Human Cases (January 2007)



FY 2006 CDC International Activities and Support



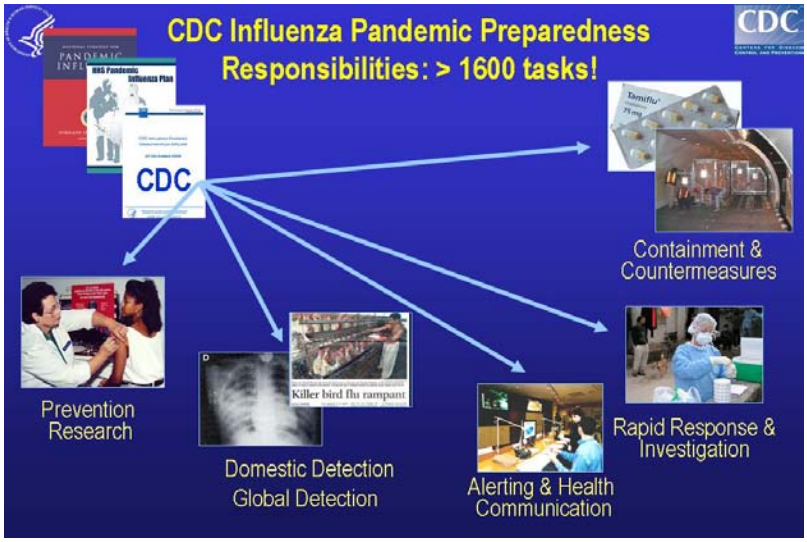
CDC Influenza Preparedness Achievements: January 2007

Vaccine & Prevention Research

- 1918 pandemic virus reconstructed
- Drug resistant H5N1 strain monitored
- Evolving H5N1 strains genetically fingerprinted
- Vaccine seed strains developed
- Extramural $$ awarded
  - $5.5 million for community protection strategies
  - $11.5 million for bedside rapid diagnostic tests
  - rapid PCR diagnostic test FDA approved
- Centers of Excellence for human / animal health funded

Rapid Detection & Response

- Secretary's 50+ State Summits
- CDC, state, local, tribal, territorial "crawl walk run" exercises
- 31 M antiviral treatments to states; > 250,000 to international reserve
- > 150 million masks and respirators stockpiled
- Enhanced global detection & rapid response
  - $65 million to target countries
  - CDC experts deployed
  - Rapid response teams trained and exercised



Senator HARKIN. Dr. Fauci.

STATEMENT OF DR. ANTHONY S. FAUCI, M.D., DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, NATIONAL INSTITUTES OF HEALTH, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Dr. FAUCI. Thank you very much, Mr. Chairman, Senator Specter, members of the committee. I appreciate the opportunity to meet with you today and to discuss very briefly with you the NIH's biomedical research efforts to attain some of the goals that have just been articulated by Dr. Parker and Dr. Gerberding.

As you know from other testimonies before this committee, what we do at NIH is based fundamentally on sound basic research principles which we rapidly try to extrapolate into clinical and applied research for the development and testing of the products that were just mentioned. In the case of flu, those products are therapeutics, diagnostics, and vaccines as you just heard. I've discussed those in detail in my written statement. What I'd like to concentrate on in the next couple of minutes is the area of vaccine preparedness for influenza.

The point I want to underscore is that which was alluded to just a moment ago by Dr. Gerberding. When we talk about preparedness, we talk about preparedness for influenza with very little distinction between seasonal and pandemic influenza. We're not talking about only H5N1 today. We're talking about our capability to respond to influenza, be it a seasonal influenza—which, I might add, and we've discussed this in the past, is not taken as seriously by society as it should be, and for that reason our preparedness has not gone into the 21st century where it belongs, but we're getting there. This is closely related, so that everything we do with pandemic influenza applies to seasonal influenza and vice versa.

Let's talk a bit now specifically about the current threat of H5N1. When we talk about making a vaccine, it's important to talk

about a pre-pandemic versus a pandemic vaccine. Right now we're looking at H5N1s that are circulating, multiple clades. We spoke about the Vietnam clade 1. There's the Indonesian Clade c.

We've done clinical trials which I'll talk about briefly, and you'll hear from Dr. Treanor, about developing a vaccine to have available, to be able to get a head start. If in fact we do, and we hope we never do get a pandemic, we need the capability of what Dr. Gerberding just said, of being able to rapidly use what we've developed to get the doses available within a reasonable period of time of several months.

Let's move on to the next slide, and we look at the trial that has gotten some attention, and that is looking at the Vietnam strain H5N1 I presented to this committee several months ago. Let me just tell you where we are today.

This is a vaccine in which there is good news and sobering news. The good news is that it induces an immune response that you would predict by laboratory parameters to be protective. The sobering news is that this occurs in about 50 percent of people, not enough, and the dose that's required to get us there is prohibitively high. So we need to figure out a way, how we can get those doses expanded and how we could learn from this.

So what are we doing from a research standpoint? What we're doing is that we are adddressing major challenges. One you've heard of. We have got to get the technology of upsurging. We've got to move from egg-based to cell-based production, but we've got to go beyond that. We've got to develop novel vaccine approaches, recombinant approaches, synthetic approaches, vector approaches, the kinds of things that are in the research stage right now, that need to be rapidly moved into practicality.

You've heard about dose-sparing strategies such as adjuvants, and also we need to optimize what we do with live attenuated vaccines. Let's just spend a half a minute on adjuvants. What is an adjuvant? We talk about it a lot. It's a compound that enhances or amplifies the body's natural immune response to what you challenge it with. It is given in several other vaccines. We have never used it effectively in influenza.

So what we're trying to say is that when you use an adjuvant, you give it together with the vaccine, it can reduce the amount of antigen needed, which can get us out of the impracticality of the high dose. It promotes earlier, stronger, and more durable responses, and it may actually—we're working on that now—increase the cross-protection, so that this is what you might get without an adjuvant and this is what you get with an adjuvant.

Very briefly, next slide, the concept of a universal vaccine, what do we mean by that? Each year as the virus changes a bit in seasonal influenza, to get optimum protection we need to get a new vaccine that's slightly modified. Why? Because what changes are these two. I know this is a complex slide, and I apologize for it, but actually it is simple if I can just walk through in about 15 seconds with you.

The H and the N are the flagship signatures of the virus, we call it H5N1, H3N2, this is what we make our vaccines against. It changes a little bit from year to year, and a lot from pandemic to pandemic. There are components of the vaccine, such as the nu-

clear protein, the matrix proteins, which change hardly at all from season to season, and also very little from pandemic to pandemic.

So we're putting a lot of resources right now into trying to get a vaccine that would induce an effective response against those components of the vaccine that don't change. Now you might ask, "Why doesn't that happen naturally?" The reason is, when the body sees these proteins, it sees it in a form that's very poorly immunogenic. In other words, it doesn't make a good response against it. Our task, from a research standpoint, is to make the body see that as something that it really wants to respond to, and we could talk about that more in the question period.

PREPARED STATEMENT

Final slide, getting back to the theme, everything that I spoke about in the few minutes I had applies to both seasonal and pandemic influenza. If we succeed, both from a production capability and a fundamental concept research standpoint, it will benefit the preparedness for both seasonal and pandemic influenza.

Thank you, Mr. Chairman. I'd be happy to answer questions later.

[The statement follows:]

PREPARED STATEMENT OF DR. ANTHONY S. FAUCI

Mr. Chairman and members of the subcommittee, thank you for the opportunity to speak to you today about the ongoing threat of a human influenza pandemic, the immediate threat from H5N1 avian influenza, and research being conducted and supported by the National Institutes of Health (NIH) that is improving our ability to respond effectively not only to an influenza pandemic, but to seasonal influenza epidemics as well.

Seasonal outbreaks of influenza occur almost every year in the United States and impose a substantial burden of morbidity and mortality on the population. Influenza viruses circulate constantly around the globe, and influenza cases occur sporadically throughout the year. Influenza epidemics, in which the number of cases peaks sharply, usually occur in winter months. These seasonal epidemics cause an annual average of about 200,000 hospitalizations and 36,000 deaths in this country, mostly among people aged 65 years and over and those with chronic health conditions. Globally, an estimated 250,000 to 500,000 influenza-related deaths occur each year.

As influenza viruses circulate, the genes that determine the structure of their surface proteins undergo small changes called mutations. As these mutations accumulate (a process called "antigenic drift"), the immunity created by prior exposure to older circulating influenza viruses or by prior vaccination no longer can reliably prevent infection. Antigenic drift is thus the basis for the predictable patterns of seasonal influenza seen in most years and is the reason that we must update influenza vaccines annually.

Influenza viruses also can change more dramatically. For example, viruses sometimes emerge that can infect species other than their natural animal reservoirs, typically migratory waterfowl. These avian viruses may begin to infect domestic poultry, farm animals such as pigs, or, very rarely, humans. When an avian influenza virus develops the ability to infect humans, the result is usually a "dead-end" infection that cannot readily spread further in the human population. However, the virus could mutate in ways that allow human-to-human transmission to occur more easily. Furthermore, if an animal influenza virus and a human influenza virus were to simultaneously co-infect a person or animal, the two viruses could exchange genes—a process known as reassortment—resulting in a virus that may be readily transmissible between humans and against which the human population may have no pre-existing immunity. When such an "antigenic shift" occurs by either of these mechanisms, mutation or reassortment, a global influenza pandemic can result.

Historically, pandemic influenza is a proven threat. In the 20th century, influenza pandemics occurred 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 world-

wide, including more than 500,000 people in the United States, and caused enormous social and economic disruption. In all three of these pandemics, for reasons that remain unclear, a much greater proportion of young adults were killed than is typical of seasonal influenza. Given this history, we can expect that a new influenza virus will emerge and another pandemic will occur at some point in the future. Although the precise timing of the next pandemic remains unknown, when it arises it is likely to spread rapidly in our modern society. The consequences likely will be severe throughout the world, in developed nations but especially in poor countries that do not have adequate public health systems.

Of known influenza viruses, the highly pathogenic H5N1 avian influenza virus currently spreading among domestic and migratory birds in Asia, Africa, and the Middle East is of greatest concern. Although the H5N1 virus remains primarily an avian pathogen, 269 people are known to have been infected, usually from direct contact with infected poultry; 163 of the people diagnosed with H5N1 avian influenza infection have died. At this time, the virus does not efficiently spread from birds to humans, and transmission from one person to another is rare. However, if the H5N1 virus mutates further or exchanges genes with a human influenza virus to acquire the ability to spread from person to person as efficiently as the viruses that cause seasonal influenza epidemics, a human pandemic could become a reality. The degree of threat from such a virus would depend on the extent to which the virus retained its current virulence and how transmissible it became.

In late 2005, the President announced the National Strategy for Pandemic Influenza, and U.S. Department of Health and Human Services (HHS) Secretary Michael O. Leavitt released the HHS Pandemic Influenza Preparedness and Response Plan, an integral component of the National Strategy. These two documents are part of a blueprint for a coordinated national effort to prepare for and respond to a human influenza pandemic that includes a National Implementation Plan and preparedness and response plans from other federal agencies. Within HHS, the National Institutes of Health, and the National Institute of Allergy and Infectious Diseases (NIAID) in particular, were given primary responsibility for the conduct of scientific research and clinical trials to foster development of therapies, diagnostic tests and devices, and vaccines to help prepare for a potential human influenza pandemic.

In my testimony today, I will present an overview of the ongoing scientific research and development efforts of NIH and our progress and priorities in creating the countermeasures needed to reduce the threat posed by both seasonal and pandemic influenza.

BASIC RESEARCH

NIH supports numerous basic research projects intended to increase our understanding of how influenza viruses replicate, interact with their hosts, stimulate immune responses, and evolve into new strains. Although many questions remain unanswered, results from these basic research studies are laying the foundation for the design of new antiviral drugs, diagnostics, and vaccines, and are applicable to seasonal epidemic and pandemic strains alike. For example, NIH-supported scientists recently used a massive database to complete the most comprehensive analysis to date of the critical sites on influenza viruses that are recognized by the immune system. Because the work reveals at the molecular level exactly where the immune system targets the viruses, it will help scientists design new vaccines, diagnostics and immune-based therapies against influenza. Moving from the molecular to the population level, NIH-supported modeling studies of the dynamics of influenza infection in large human populations are providing important insights into how the virus spreads, the effects of air travel and commuting patterns on how fast epidemics move, and the potential value of antiviral drugs and nonpharmaceutical interventions in controlling outbreaks. In addition, several NIH programs are describing the detailed immune responses to seasonal influenza vaccination in humans to define the immune correlates of protection and to understand the lack of efficacy in the elderly and other immunocompromised individuals.

To better understand the varied and ever-changing genetic blueprints of influenza viruses, NIH launched the Influenza Genome Sequencing Project in the fall of 2004. The goal of this collaboration between NIH (NIAID and the National Library of Medicine), St. Jude Children's Research Hospital, the Wadsworth Center, the Institute for Genomic Research, the Centers for Disease Control and Prevention (CDC), and several other organizations is to determine the complete genetic sequences of different influenza viruses from around the world and to rapidly provide these sequence data to the scientific community. The project has determined genomic sequences of close to 2,000 animal and human influenza viruses, all of which are freely available to researchers via the NIH website; more than 200 new sequences are

being added every month. The data flowing from this program will enable scientists to track how influenza viruses evolve as they spread through their host populations and across geographic regions, and to match viral genetic characteristics with virulence, ease of transmissibility, and other clinical properties. The end result will be a clearer understanding of how influenza epidemics and pandemics emerge.

Scientists also are working to understand the virus that caused the devastating 1918 pandemic, and in the process are gaining new insights into what might happen with the H5N1 avian influenza virus. Using pathology samples from victims of the 1918 pandemic, NIH intramural and extramural scientists and their collaborators have determined the complete genetic sequence of this virus, and have assembled viruses that bear some or all of these genes. The sequence revealed that the pandemic virus probably did not arise through a reassortment of animal and human viruses but rather was an entirely avian-like virus that adapted to infect humans. Infection of mice and non-human primates with the complete 1918 virus resulted in a damaging inflammatory response in the lungs, with aberrant levels of expression of immune regulatory molecules. This result might explain the extraordinary mortality among young adults in the 1918 pandemic because young adults have a strong and robust immune system and a stronger immune response would lead to increased pathological consequences. Of note, immunological responses similar to those seen with reconstructed 1918 viruses in animals have been seen with recent H5N1 virus infections in humans.

Ongoing sequence analysis of human influenza viruses from before and after 1918 seeks to place the emergence of the 1918 virus in its historic context. Understanding how long the pandemic virus circulated in humans before it emerged in full force in 1918 has important implications for pandemic planning, including more effective nonpharmaceutical interventions. Knowledge of how highly virulent influenza viruses kill could lead to new strategies for the development of novel antiviral drugs and other therapies.

VACCINES

Vaccines are essential tools for the control of influenza. NIH efforts to facilitate the creation of effective H5N1 influenza vaccines are based on isolates of the currently circulating H5N1 virus. Since there is no H5N1 pandemic among humans at this time, such vaccines are referred to as pre-pandemic H5N1 vaccines. Should an H5N1 virus emerge that can be easily transmitted among humans, a vaccine based on the newly emerged strain would need to be developed. However, development of pre-pandemic H5N1 vaccine candidates, which is proceeding rapidly, serves two important purposes. As the H5N1 virus mutates, even imperfectly matched prototype vaccines may prime the immune system to respond to related H5N1 viruses and offer enough protection to reduce the severity of disease, and therefore serve as an important preliminary component of pandemic control. In fact, recent results from a small study indicated that a previously administered dose of H5N1 vaccine successfully served as immunologic priming for a vaccine against an antigenically drifted strain given seven to eight years later. Such a strategy could buy precious time while a vaccine that more closely matches the pandemic strain is produced and distributed. Producing prototype H5N1 vaccines also provides an opportunity to create the infrastructure, processes, and production capacity to manufacture enough vaccine should a worldwide pandemic ensue.

In early 2004, NIH-supported researchers used a technology called reverse genetics to create an H5N1 reference vaccine strain from a Vietnamese H5N1 isolate. NIH then contracted with sanofi pasteur and Chiron Corporation to use this reference strain to manufacture small-scale lots of inactivated virus vaccine for use in clinical trials. These pre-pandemic vaccine candidates have now been clinically tested in healthy adults, elderly people, and children, and the results provided both good and sobering news. The good news is that the vaccine is well tolerated, and induces an immune response that is similar in all age groups and is suggestive of protection against infection with the immunizing strain. The sobering news is that the doses of vaccine needed to elicit the levels of immune responses usually thought to predict protection were larger than those used for seasonal influenza vaccines. In addition, these predictably protective responses were elicited in only approximately half of the vaccinated individuals. The need for larger doses of vaccine reduces the number of people who could be immunized with the amount of vaccine that can be produced in a given timeframe. In addition, it is important to elicit a protective immune response in a greater percentage of vaccinated individuals.

We, therefore, have pursued the use of vaccine additives called adjuvants that amplify the immune response. Results from a Phase I clinical trial of a candidate vaccine for H9N2 influenza—another avian virus that has caused human deaths—indi-

cated that an adjuvant called MF59 increases the immune response and could thus reduce the required dose. In 2006, GlaxoSmithKline announced encouraging results indicating that its H5N1 influenza vaccine, using a proprietary adjuvant, achieved a high immune response at a low dose of antigen. Preliminary results from NIH-supported clinical trials of H5N1 pre-pandemic vaccine with adjuvants will soon be available. In addition, NIH-supported basic research into a family of immune system proteins called Toll-like receptors—molecules that are among the immune system's "first responders"—is providing important insights into how adjuvants work, and may illuminate new opportunities for improved dose-optimization strategies. In addition, recent research has shown non-Toll-like receptors to be potential new targets for adjuvant function. This finding and other promising approaches to developing new vaccine adjuvants are being studied by NIH-supported innate immunity research programs.

Most current seasonal influenza vaccines are based on an inactivated influenza virus grown in fertilized chicken eggs. Unfortunately, the domestic capacity for the manufacture of influenza vaccines using egg-based technology can meet only a small fraction of the expected demand should a pandemic virus emerge today. For this reason, we are conducting research that will help to increase U.S.-based pandemic influenza vaccine production capacity, and lead to the further development of new vaccines and manufacturing methods that are faster and more flexible for influenza vaccine production. The ultimate goal is to have the capacity to produce sufficient quantities of effective and safe pandemic influenza vaccine to protect every American within six months of the emergence of a new pandemic virus.

Although egg-based manufacturing methods have served us well for more than 40 years, they are logistically complex, can lead to delays if the vaccine strain of influenza virus will not grow efficiently, and cannot be rapidly expanded in response to increased demand for vaccine. To build a more reliable domestic manufacturing capacity that could be rapidly mobilized in response to the emergence of a pandemic virus, we are working to expand and accelerate the development of additional manufacturing methods, such as growing the vaccine strain in cell culture. New technologies for producing influenza vaccines in cell cultures are promising and such technologies are currently used in licensed vaccines for other diseases. However, the successful development of production methods and licensure of influenza cell-based products are likely several years in the future, and therefore, support for current egg-based technologies should also continue.

Our strategic plans have articulated the goal of developing the capacity to provide 300 million people in the United States with the needed doses of pandemic vaccine within a six-month time frame. Our success in reaching this goal will depend to some extent on the success of efforts to understand and expand the use of effective and safe adjuvants and other dose-optimization strategies, and efforts to develop other technologies for vaccine preparation.

In this regard, NIH is collaborating with industry to pursue several other vaccine strategies in addition to inactivated virus H5N1 vaccines. From the mid-1970s to the early 1990s, NIH intramural and extramural researchers developed a cold-adapted, live attenuated influenza vaccine strain that led to the product now marketed by MedImmune, Inc. as FluMist®. NIH intramural researchers are now working with colleagues from MedImmune Vaccines under a Cooperative Research and Development Agreement to produce and test a library of similar live vaccine candidates against all known influenza subtypes with pandemic potential, allowing a head start and faster response should a strain from any of these subtypes emerge as a pandemic threat. Tests in mice and ferrets showed that two doses of a live attenuated H5N1 candidate vaccine protected the animals from infection and death by a wide array of H5N1 isolates—an encouraging result indicating that this type of vaccine might protect even if not precisely matched to the circulating strain. Human studies of candidate cold-adapted, live attenuated H5N1 vaccines are underway.

Other strategies under development include recombinant subunit vaccines, in which cultured cells are induced to make various influenza virus proteins that are then purified and used in a vaccine; DNA vaccines, in which influenza genetic sequences are injected directly into a person to stimulate an immune response; and approaches that insert the genes of influenza virus into a different, harmless virus (a "vector") that is used as a vaccine. A human trial of a DNA vaccine, developed at the NIAID Vaccine Research Center and designed to prevent H5N1 infection, began last month at the NIH Clinical Center. Planning is also underway to test intradermal injection as an alternate delivery technique for this vaccine, and to evaluate alternative vaccine candidates, such as recombinant adenoviral vectors containing H5N1 genetic sequences and recombinant H5N1 proteins.

An important NIH research goal is to develop a vaccine that raises immunity to parts of the influenza virus—so called epitopes—that vary little from season to season and from strain to strain. This is a challenging task because the invariant epitopes of influenza viruses generally do not elicit a vigorous immune response. Nonetheless, there is a great deal of interest in so-called Vaccine Common Epitope (VCE) vaccines against influenza, especially based on the influenza M2 protein. The fundamental strategy is to present the common antigen to the immune system in a way that stimulates a robust and protective immune response. Such a vaccine might not only provide continued protection over multiple seasons but also might offer considerable protection against a newly emerged pandemic influenza virus. This would substantially increase the overall immunity of the population to influenza A, and make the country far less vulnerable to a new influenza A virus.

ANTIVIRAL THERAPIES

Antiviral medications are an important counterpart to vaccines as a means of controlling influenza outbreaks, both to treat infection after it occurs and under certain circumstances to prevent infection prior to or immediately after exposure. Four drugs currently are available for the treatment of influenza, three of which are also licensed in the United States for influenza prevention in certain populations. Efforts to test and improve these existing anti-influenza drugs are in progress. H5N1 strains circulating in Southeast Asia, Africa, and elsewhere are generally resistant to two older drugs—rimantadine and amantadine—but the majority of isolates are sensitive to a newer class of drugs, called neuraminidase inhibitors. This class of drugs includes oseltamivir (marketed as Tamiflu®), currently approved for treatment and prophylaxis of individuals older than one year. Studies to test the efficacy of higher doses of neuraminidase inhibitors, and to further characterize the safety profile of oseltamivir in very young children, are in the advanced planning stages. NIH is also collaborating with the Department of Defense and Department of Veterans Affairs (VA) in a VA-funded research project to examine if probenecid co-administration with oseltamivir can increase the effective supply of oseltamivir. In addition, NIH has collaborated with the World Health Organization, the Wellcome Trust, and other institutions in Indonesia, Thailand, Vietnam, and the United Kingdom to develop the South East Asia (SEA) Influenza Clinical Trial Network, which is developing in-country research capacity in a region directly affected by the H5N1 influenza outbreak and conducting studies of antivirals in people infected with the H5N1 virus.

NIH-supported research to identify additional anti-influenza drugs that work through a variety of mechanisms is progressing rapidly. An NIH program that screens both licensed compounds and new drug candidates—first in cell culture systems and then in animal models—has identified several promising anti-influenza candidates. NIH is collaborating with the private sector to further develop three promising candidates out of the 32 that were screened in mice in 2006:

—FluDase binds host cell receptors to prevent viral entry;

—T–705 inhibits replication of viral RNA; and

—Peramavir inhibits viral neuraminidase.

Furthermore, NIH is collaborating with industry to develop novel, broad-spectrum therapeutics that might work against many influenza virus strains; some of these target viral entry into human cells, while others specifically attack and degrade the influenza virus genome. In animal models, treatment with a monoclonal antibody is effective against what would otherwise be a lethal dose of H5N1 virus, even if given up to three days after infection, indicating that passive administration of antibodies might be a useful strategy to contain an H5N1 pandemic. NIH is exploring the possibility that one may be able to develop a high-titer anti-H5N1 antibody preparation as a treatment for patients with avian influenza through the hyperimmunization of healthy volunteers. Studies are also in progress to evaluate long-acting next-generation neuraminidase inhibitors. The development and testing in animals of combination antiviral regimens against H5N1 and other potential pandemic influenza strains is also a top research priority.

DIAGNOSTICS

Inexpensive, fast, accurate, and precise methods to diagnose influenza infection in its earliest stages continue to be a focus of ongoing research. If a pandemic influenza virus were to emerge, diagnostic tools capable of quickly and definitively identifying infected people would be extremely valuable, helping to slow the spread of the virus and maximizing the efficiency with which stockpiled antivirals are used. If available for routine use, such diagnostics would also help to diagnose and treat seasonal influenza, which clinically can mimic many other diseases.

Recently, NIH-supported scientists from the University of Colorado at Boulder, working in collaboration with researchers at the CDC, showed that a potentially revolutionary diagnostic device, called the MChip, is capable of quickly identifying many influenza viruses, including H5N1 avian influenza. The MChip has a number of strengths that could allow it to become a valuable tool in global influenza control efforts. The materials for each chip cost less than ten dollars. It tests for the influenza matrix gene, which varies relatively little between strains and over time, so the test likely would not have to be updated as frequently as tests based on other genes. The researchers already have automated the process of reading the test's output, allowing accurate assessment of many samples in a short time. Discussions are already under way to commercialize its manufacture, and in the future researchers hope to adapt this technology for handheld field use.

CONCLUSION

In closing, I would like to emphasize that our efforts to successfully prepare for an influenza pandemic—with a sufficient supply of effective vaccines and antiviral drugs, efficient infection control, and clear public communication—will benefit our ability to cope with seasonal influenza. It is clear, however, that we have not yet optimized our preparedness and responsiveness to this recurring disease. There is a pressing need to move toward adoption of newer vaccine manufacturing techniques and other strategies that can improve the surge capacity, flexibility, and speed with which vaccines are made. Moreover, increasing the proportion of the population that is vaccinated annually with seasonal influenza vaccine will help to pave the way for the more intense vaccination effort that would accompany an influenza pandemic.

Fortunately, much of the research on influenza vaccines and antivirals that has been undertaken in response to the emergence of H5N1 avian influenza is directly applicable to both seasonal and pandemic preparedness, and efforts to improve our response to one will invariably improve our ability to manage the other.

Thank you for the opportunity to testify before you today. I would be pleased to answer any questions that you may have.

Senator HARKIN. Thank you, Dr. Fauci. I do want to follow up on that. I don't understand all that, but I want to get a better understanding before we leave today on this "universal vaccine" and how that might work.

Dr. Treanor, thank you very much for being here today, and we'll turn to you now.

STATEMENT OF DR. JOHN JAY TREANOR, M.D., DIRECTOR, VACCINE TREATMENT AND EVALUATION UNIT, UNIVERSITY OF ROCHESTER MEDICAL CENTER

Dr. TREANOR. Thank you very much, Chairman Harkin and Ranking Member Specter and other distinguished members of the subcommittee. I want to thank you for allowing me to testify today and for your leadership in calling this hearing on a very, very important topic.

Now, most of my comments will simply echo what Dr. Fauci has just said. I would like to tell you about the University of Rochester Vaccine and Treatment Evaluation Unit, which is one of seven NIH-sponsored units throughout the country that perform clinically related research on novel vaccines and other control measures for human infectious diseases.

This NIH-supported research has included studies of viral diarrhea, whooping cough, genital herpes, cervical cancer, respiratory viruses in children, pneumococcus, malaria, smallpox, and anthrax, among others, and has been particularly focused recently on the development of vaccines for both seasonal and pandemic influenza. I think that while this research has made substantial progress in guiding the use of currently-available measures, it's clear that we have a lot more to learn to be able to effectively deal with both sea-

sonal and pandemic flu. I would certainly echo what Dr. Fauci has just said, that what we learn about seasonal and pandemic flu are intrinsically linked to each other.

Now, as you have heard, the initial approach to developing a vaccine was really focused on using something similar to what we used for conventional flu, because we know those vaccines are safe and do have some efficacy in reducing flu. But we have also learned that in the case of H5, relatively high doses are required. This would be a strategy that would be effective in selective groups, but to provide protection for a large population we need to find ways to use lower doses, and one of those ways is through the use of adjuvants.

Aluminum is the most commonly used adjuvant for vaccines now, but through these NIH studies we've learned that aluminum does not appear to substantially improve the response to an influenza H5 vaccine. So attention has been turned to other adjuvants and some promising candidates have been identified, including the adjuvant MF–59, which has been demonstrated in the VTEU studies to effectively increase the response to both H5 vaccines as well as another pandemic candidate, H9.

Now, one of the other interesting things we've learned is, as you know, with the regular flu vaccines we only need to give a single dose and we get a fairly good response. With H5 that doesn't work, and one of the reasons is that for regular flu vaccines the immune response has been primed by multiple previous exposures to related viruses.

We found that when we looked at people who had been vaccinated against H5 viruses back in 1998 and gave them a single additional dose of the H5 vaccine in 2005, they had a very vigorous immune response, suggesting that they had been primed. These sort of prime-boost strategies would be another way potentially to vaccinate at least selected populations who are at high risk of exposure prior to a pandemic.

Now, as you have heard, one of the dreams of influenza researchers for many years has been development of a universal flu vaccine that would be able to provide protection against all strains of influenza, and there has been substantial progress in this area. At least one of these vaccines, based on the M2 protein, is in active clinical development.

But all of the data that supports the use of a universal vaccine has really been generated in animal models of influenza. We do know from prospective studies in families that some degree of cross-protection between strains does occur, but we don't understand completely the immune mechanisms which are responsible for those cross-protective responses.

One of the things we'd like to learn a lot more about is the immune response to the very first exposure to influenza in children and how that modifies subsequent responses when people are reexposed. These kinds of studies would have been very difficult to do many years ago, but NIH-supported advances in the ability to study the human immune response I think now create the possibility to learn much, much more about the immune response to flu and how to manipulate this to create a truly universal vaccine.

So, in summary, I think research supported by NIH has led to developments that will significantly enhance our ability to respond to a pandemic in the short term, and much more work is needed for long-term approaches. I don't think there is a clear leader or an ultimate long-term solution at this time, although many promising methodologies are being developed.

I think the most effective long-term strategy for improved influenza vaccination for both pandemic and seasonal flu is continued investment in basic research in both virology and immunology of influenza, with rapid translation of lead candidates into well designed and carefully controlled clinical studies.

PREPARED STATEMENT

I'd like to thank the committee and sincerely let you know how much we in the research community appreciate the support that you've shown us with your continued appropriations and support for the struggle to battle both seasonal and potential pandemic influenza. Thank you.

[The statement follows:]

PREPARED STATEMENT OF DR. JOHN JAY TREANOR

Chairman Harkin, ranking member Specter and other distinguished members of the subcommittee: Thank you for allowing me the opportunity to testify today. I would also like to thank you for your leadership in calling this hearing on this very important topic.

I would like to begin by briefly presenting our work at the University of Rochester Vaccines and Treatment Evaluation Unit (VTEU) related to vaccines for pandemic influenza and some of the issues to consider in this context. The University of Rochester VTEU is one of 7 NIH-sponsored units in the United States that perform clinically oriented research on novel vaccines and other control measures for human infectious diseases. This NIH-supported research has included studies of rotavirus (the most important cause of diarrhea in children), pertussis or whooping cough, genital herpes, human papillomavirus (the cause of cervical cancer), respiratory syncytial virus, pneumococcus, malaria, smallpox, and anthrax. In addition, the unit at Rochester has been intensively involved in studies of influenza vaccines in infants and young children, healthy and elderly adults, including candidate vaccines for pandemic varieties of influenza A virus. This research has helped guide the use of the currently available vaccines, and has also identified that while progress has been made, we have a long way to go to be fully prepared for the next pandemic.

Inactivated H5 Vaccine Requires High Doses.—Two types of influenza vaccine have been convincingly demonstrated to actually protect humans against influenza: inactivated influenza vaccines, and live attenuated influenza vaccine. Our evaluation efforts for H5 have focused on inactivated vaccines made using standard technology, because such vaccines are effective for prevention of conventional or interpandemic influenza and are used safely and effectively each year. We have learned that inactivated vaccines for H5N1, while well tolerated, are poorly immunogenic and require high doses to elicit the types of immune responses likely associated with protection. The reasons for these relatively poor immune responses are unclear, but the results have been replicated over many studies. While a high dose inactivated H5 vaccine could be an effective tool for controlling pandemic influenza in selected groups, strategies using much lower doses would be required to provide enough vaccine for effective pandemic control in the general population.

Enhancing the Response With Adjuvants.—One approach to dose-sparing is the use of additional components, called adjuvants, which are designed to improve the response to a co-administered vaccine. Aluminum salts are commonly used adjuvants for many current vaccines, but our studies suggest that aluminum hydroxide is not able to significantly enhance the immune response to existing formulation of H5 vaccine. Studies of aluminum with other types of inactivated H5 vaccines are in progress. There is an urgent need to develop and clinically validate effective and safe adjuvants for use with pandemic vaccines, and a number of promising candidates have been identified. One candidate, the oil-in-water emulsion MF–59, has already been shown to significantly improve the response to an H5 vaccine as well

as an additional strain, H9, in clinical trials conducted by NIH VTEUs, and other adjuvant trials are being planned.

Revaccination and Priming Doses.—Unlike the H5 vaccine, regular influenza vaccines are given as a single dose each year, and elicit vigorous immune responses. In part, this difference is because the immune system has been primed to respond to regular flu vaccines by repeated prior exposures to related viruses. The pre-pandemic use of an H5 vaccine might prime the population to respond to a subsequent single lower dose, greatly facilitating a pandemic vaccination campaign. In a very small, preliminary study, we found that adults who had received an experimental H5 vaccine in 1998 had a much more vigorous immune response to a subsequent H5 vaccine in 2005 than did adults who had not been previously vaccinated. Similar results have been reported by workers in the United Kingdom, and suggest that a pre-priming strategy could be considered, particularly in high-risk populations. These two strategies, dose-sparing with adjuvants, and prime-boost strategies using conventional vaccines, probably represent the most promising short-term solutions to pandemic influenza.

A Universal Influenza Vaccine.—Influenza viruses continually evolve their outer coat proteins to evade the immune system, making both minor and major changes that can severely limit the effectiveness of a vaccine made against the "wrong" strain. This is an issue each year for conventional vaccines, but is also an important consideration for the H5 viruses, which are in a state of rapid evolution. For many years, influenza researchers have dreamed of a vaccine that would not be affected by these changes and could provide protection against all strains of influenza. A handful of potential targets for such a vaccine have been identified in animal studies, and one of these, the M2 protein, has reached the stage of active clinical development at Rochester and elsewhere. However, the degree to which these vaccines will provide cross-protection in humans is still unknown.

A Better Understanding of the Human Immune Response is Needed.—Almost all of the potential targets for a universal flu vaccine have been identified in studies in animal models of influenza. We know from observations in families many years ago that cross protection in humans can occur, but the immune mechanisms responsible for cross protection in humans have not been identified. Defining the immune responses of humans that could be manipulated to make an effective universal flu vaccine will require careful, prospective studies to examine both the B cell as well as the T cell components of the primary response to infection, and the consequences of these responses upon subsequent exposures to virus. The work will be expensive and tedious, but is now quite feasible with modern technologies of human immunology.

Developing a more detailed understanding of cross-protective immunity in humans could lead to significant advances in our ability to control both conventional and pandemic influenza. However, these efforts will take time, so that development of a universal influenza vaccine is best seen as a more long-term (8 to 10 year) approach to pandemic influenza.

Summary.—Research sponsored by NIH has led to developments that can significantly enhance our ability to respond to a pandemic in the short-term, but much more work is clearly needed. There is no clear leader for an ultimate long-term solution at this time, although many promising technologies are being developed. I believe that the most effective long-term strategy for improved influenza vaccination for both pandemic and inter-pandemic influenza will be continued investment in basic research in both the virology and immunology of influenza, with rapid translation of lead candidates into well designed and carefully conducted clinical studies.

In the appendix to this testimony I have outlined some additional areas of active research in the development of a pandemic flu vaccine. Again, thank you for allowing me this opportunity to testify and thank you for the continued support and resources this Subcommittee allocates to the NIH and others to help up us prepare for the predictable annual severe impact of interpandemic flu, and the unpredictable, potentially catastrophic impact of an avian flu pandemic.

APPENDIX

Antibody Tests for H5 Influenza are Not Robust.—A large number of inactivated influenza vaccines are currently in clinical trials throughout the world. It is important to recognize in interpreting the results of these trials that the assays used to assess immune responses work well for determining relative responses within the same study, but are much less well suited for comparing results between laboratories. This means that one must exercise caution when comparing the results of trials done by different groups. In addition, there is no absolute level of antibody

that has been validated as a specific correlate of protection against H5 influenza in man.

Animal Models are Not Perfect.—Several animal models can be used for pre-clinical evaluation of influenza vaccines, including the mouse, ferret, hamster, guinea pig, and monkeys. With the exception of the ferret, none of these animals are natural hosts of influenza, and all of them have significant imperfections for testing the efficacy of candidate influenza vaccines. Many different kinds of vaccines have been shown to protect mice against lethal influenza, but it is unclear to what extent this model is predictive of protection in humans.

Adjuvants Hold Promise for Dose Sparing.—There are a multitude of promising adjuvants in active clinical development. Some adjuvants rely on changing the formulation to improve presentation to the immune system, for example mixing the antigen with an oil, formulating the antigen in a lipid membrane, or adding irritants to the antigen to recruit immune cells to the site of injection. Other adjuvants directly engage the toll-like receptors (TLRs), a family of receptors that recognize molecules typically found in pathogens and serve as an early warning mechanism for the immune system. For example, we have recently noted dramatic enhancement of the immune response to a malaria vaccine when the TLR–9 agonist CPG was added to the vaccine. Combinations of both approaches may be the most promising strategy. Recently, several groups have reported that systems that physically link the antigen to the adjuvant, rather than simply mixing them together, may be even more effective.

However, none of the adjuvants tested to date has shown a dramatic effect on the response to conventional influenza vaccine in human trials. In addition, most adjuvants are associated with some increase in local pain on administration, which might make them less acceptable for routine use. Unless an adjuvanted influenza vaccine were to have a clear advantage over a more conventional vaccine for interpandemic influenza, it may be difficult to build the capacity for such a vaccine to use for pandemic influenza. In addition, there are no studies currently evaluating adjuvanted influenza vaccine in young children, who will be an important target group for a pandemic vaccine. Finally, almost all adjuvants are proprietary but would need to be shared among many manufacturers in order to be used effectively in a pandemic situation.

Alternatives to Egg Based Production are Desirable but not Sufficient.—Current vaccines are manufactured in eggs, but there is a large-scale effort underway to move this manufacturing to a cell-culture based system. Systems which involve either growing influenza viruses in cell culture or using recombinant DNA techniques to produce the relevant influenza virus proteins in a cell culture system are both in active development. While these new procedures may result in a more stable vaccine supply and one which could be increased more rapidly in response to a pandemic they do not intrinsically improve either the safety or the efficacy of the vaccine itself. These systems do represent a potential short term advantage for pandemic vaccine production. If in addition, these production methods resulted in significantly greater yields, then routine use of higher doses of vaccine associated with improved immune responses might be practical.

Live Attenuated Vaccines Mimic the Response to the Pathogen.—Fundamentally, a live attenuated vaccine consists of an influenza virus that has been genetically altered in such a way as to reduce or eliminate its ability to cause disease in the recipient. In the case of influenza, this has been done by reducing the replication fitness of the virus, and requires a careful titration to achieve a virus that replicates enough to generate an immune response, but not enough to cause symptoms. Because live vaccines amplify themselves in a susceptible host, they might be especially effective in response to a pandemic, and carefully controlled clinical trials to evaluate pandemic vaccines based on the licensed live attenuated influenza vaccine are currently underway. It is too early to tell whether these vaccines will generate good immune responses to the H5 viruses. Multiple other potential live attenuated vaccine viruses are in various stages of development.

A Replicating Antigen Triggers a Different Response.—When a vaccine antigen is actually synthesized in the cells of the recipient, as would be the case upon exposure to the pathogen, the antigens are presented to the immune system in a fundamentally different way than an inactivated vaccine. In addition to using a live vaccine, this can be accomplished by cloning the gene for the relevant protein into another attenuated virus or bacteria and using that agent as a vector for delivery of the vaccine. Several approaches for using vectors for delivery of influenza antigens to the immune system have shown promising results in various animal models. Vectored vaccines can be problematic for use in a situation where vaccines must be periodically readministered because development of immunity to the vector can limit their effectiveness. Vectors which simply deliver the gene and undergo limited replication

in the host can circumvent this problem in some cases. Vectored influenza vaccines are promising but have not been validated in studies to show that they can prevent influenza in humans.

DNA Can Stimulate an Immune Response.—An alternative to using a vectored approach is the use of DNA encoding the antigen of interest. Because DNA is relatively easy to synthesize, these vaccines could theoretically be produced in large quantity and quite rapidly. DNA vaccines in humans have generally been more effective at generating cellular immune responses than at generating antibody, and this is a major drawback for a disease like influenza where the principal modality of protective immunity is felt to be antiviral antibody. However, recent results using powder delivery of the DNA into the skin has been reported to generate detectable antibody responses to influenza in phase I studies and additional clinical trials including studies of DNA vaccines for H5 influenza are underway in both the United States and the UK. Significantly more data will be required before these vaccines can be considered a mainstream approach for pandemic control.

Induction of Mucosal Immunity May Provide Enhanced Protection.—Influenzavirus replication in man is restricted to mucosal surfaces, an area of the body served by a specialized immune system. Approaches to specifically target mucosal immunity are highly effective in animal models, and provide good cross protection through poorly understood mechanisms. Live vaccines are one approach to inducing mucosal immunity against influenza. Other approaches which couple intranasal administration of protein antigens or virus-like particles with mucosal adjuvants are also in development, but several years away from clinical deployment.

Pandemic Approaches Must Also Work for Conventional Influenza.—A major challenge for the sustained development of a pandemic vaccine is that in order for these vaccines to be produced in quantity, they likely must be commercially viable for seasonal use. This important issue must be considered for all of the experimental approaches currently in development for a pandemic vaccine.

Senator HARKIN. Dr. Treanor, thank you very much. Thank you all very much.

I just got notice that there's going to be two rollcall votes starting around 11:30, so we'll try to wrap up everything in the next hour or so. We'll do 5-minute rounds of questions, then we'll come back around for the second round. I'll start my 5 minutes right now.

Dr. Gerberding, you've traveled a lot in Asia. You showed us the slides up there. I hear bits and pieces of conversation. People wonder, well, you know, you get a flu shot, you get a flu shot and that's fine, and there seems to be a lessening of any kind of real concern about this avian flu. Again, tell us, why is this avian flu different than what we know of as the flu? You know, people get the flu and they say, well, you get over it, or you get a shot. Why is this different? Is it more virulent? Why is that?

Dr. GERBERDING. This is a very virulent flu. When we have seasonal flu, the mortality rate is certainly less than 3 percent. We're talking here about a virus that when it does affect people, has a mortality rate of greater than 50 percent, so that is in and of itself a reason for great concern.

But, more importantly, people do not have any immunity to the H5 virus, so we have to assume that basically everyone in the world is susceptible. That means if it did evolve to be efficiently spread, we would all be at risk for disease and potential death if we had a mortality rate that was anywhere near what it currently is. Generally, as viruses evolve, they adapt to people and they become less deadly, but there's no guarantee that that would be the case. So it's alarming, we're not protected from it, and it's alarming because it is so deadly.

Senator HARKIN. In these areas where we've had this outbreak in humans, have we had any experience with using any antivirals afterward, and have they been successful?

Dr. GERBERDING. It's very difficult to say how well the families, the two families of antivirals work for H5N1 in people because they're not coming to treatment early enough to expect a benefit. Even for regular flu, you have to treat within the first 48 hours of feeling sick before you get any benefit, so these are late treatments. There's some suggestion that they may be helpful. There's also a suggestion that if you treat people, their virus can develop a resistance to the drugs. So we have a lot to learn about the role of antivirals for avian flu.

Senator HARKIN. A more general question, Dr. Gerberding, and that is I guess back to developing the capacity. We're spending money, a lot of money, on that. My concern is, what's going to happen if we create the capacity but there is no demand out there for the annual flu shot?

Now, I hear you on the radio advising people to get their flu shots. I followed your advice and got my flu shot, but there seems to be some reticence among a lot of people in this country at getting their flu shots. If you're going to build the capacity, then you want to get people to get their annual flu shots, and I just wonder if you have any thoughts on that next step and what we can do besides your urging everyone.

Dr. GERBERDING. I think we have every year expanded the number of people that we know can benefit from a flu shot, so the number of people who need to be vaccinated based on science has continuously grown. In fact we have continuously increased the number of people that we vaccinate, but we're not anywhere near the number that need to be vaccinated.

Senator HARKIN. Are you experimenting with any new delivery type systems?

Dr. GERBERDING. We are not experimenting with new delivery for seasonal influenza.

Senator HARKIN. That's what I mean, just for seasonal.

Dr. GERBERDING. We have some progress underway with an NIH study to look at better ways of delivering H5 vaccine, but right now with the licensed products they're being delivered conventionally.

Senator HARKIN. Okay. Thank you.

Again, Dr. Fauci, again I want to get a better understanding of this universal vaccine and priming. Tell me again what it means to be primed.

Dr. FAUCI. Sure. To be primed is when you—there are several ways of priming. You can be primed naturally, in the sense of what Dr. Gerberding mentioned. So let's say 3 years ago I got exposed to an H3N2 seasonal influenza, got mildly ill because I had some background immunity, and then this year I get exposed, without necessarily being vaccinated, to a related H3N2 seasonal influenza. I likely would do much better than someone who had never before been exposed to an H3 because I was naturally primed with a previous infection.

When you deliberately, artificially prime somebody, it refers to what Dr. Treanor was mentioning, that you give a shot which is a first or prime shot. It sort of revs up the immune system so that when you get the next shot, which is the boost, or you get exposed and get boosted, then you already have what we call immunological

memory to allow you to respond more quickly to something that you've already seen before. That's exactly what priming means.

Now, with regard to the universal vaccine, this is not going to be an easy thing, because if just mere exposure to those components of the virus that don't change was going to protect you, then everyone who was previously exposed to influenzas would be protected.

So what happens is that if you look at the virus, if you blow it up—and that's what I try to do with that schematic—and you look at all the different proteins, which are the things that the body sees, when the body sees those proteins it makes a response against it, so that the next time you get exposed to the real virus it will rapidly respond. It relates to your first question about priming.

There are components of that virus that change naturally from year to year. It's called drift. They change a little bit, not enough to make it a different virus but enough to require that if you want optimum protection, you're going to have to change your vaccine to look a lot more like the virus. Yet there are also components to the virus that just don't change from one season to another, or even from one pandemic strain to another, such as the NP—it doesn't mean anything to anybody except as a designation, nuclear protein—and M for matrix. They stay relatively the same.

So you ask a logical question: Now, wait a minute. If this doesn't change, why don't we make that the target of our vaccine? That's exactly what we're doing, but the issue is that the way the body naturally sees it, it just doesn't make a good immune response against it because the way it's programmed, it doesn't recognize it in what we call—a big word—an immunogenic form, in a form that would really tell the body, "Hey, make a response against me."

So we manipulate that molecule, present it to the body, and say we're going to see what happens if you make a very good response against that antigen that doesn't change from virus to virus. If it does make a good response, then you have the possibility of protection against all the strains, hence you use the word "universal" vaccine.

Senator HARKIN. Very enlightening. Thank you very much, Dr. Fauci.

Senator Specter.

Senator SPECTER. Thank you, Mr. Chairman.

I'm concerned that there is not as much public awareness or concern today as there was a year ago. A year ago we had John Barry talking about his book, "The Great Influenza," and there were a great many articles. There was a great deal of publicity, and that was helpful in getting the significant appropriation, but now the matter has tapered off. There is not the public awareness. You see an occasional article, but I don't think the public understands how serious the potential for it is, and that's why this hearing is so important.

When you take a look at the charts, and I thank you, Dr. Gerberding, you see the impact on humans, relatively small, in red, 269 cases since 2003 and 163 deaths, but the potential where the birds have been affected is much, much greater. So I think it would be useful if there was an assessment as to how serious is the risk.

Now I know that that's very difficult to answer in a scientific way and you don't want to unduly alarm people, but on this state of the record I think people are now unconcerned, and I think that there needs to be some practical information put out as to what people do. Should we store water in our homes? Should we have staple foods? What is the extent of the risk if you leave your house to go to the grocery store?

We've had advice that you ought not to go to the movies or you ought not to go where there are large groups of people. Should employers start to make plans to communicate with their employees at home through their Blackberrys, to try to keep the Senate and the House going, businesses going?

Then there is the question as to when do we get the shot. You can't get the shot now because you don't know what the strain is, but when will we know the strain?

Now I know I've asked a whole series of questions, but within 5 minutes you can't cover all the questions and get answers, but those are questions which I would like you four professionals to address. C-SPAN is a good medium. People will be watching this. You have to be an insomniac. They always play the Harkin-Specter hearings at 3 a.m.

But let me ask you, Dr. Gerberding, and you, Dr. Fauci, what can be done by way of addressing the risk assessment so that it is both realistic and it alerts people to the danger? Then what can be done by way of something that is written and in simple form to tell people what they ought to do now, if anything, for prevention. When they ought to start to look for a vaccination, and what employers ought to do and organizations ought to do to try to keep functioning if it does strike? Dr. Gerberding, would you start, please?

Dr. GERBERDING. Thank you. Thank you because you're right, that having an opportunity to be on C-SPAN or to know that Congress is paying attention to this really helps us. People who fail to prepare for a flu pandemic are going to be tragically mistaken in retrospect. It's inevitable that we will have a pandemic. It may have nothing to do with H5N1 virus, and that——

Senator SPECTER. Dr. Gerberding, let me interrupt you there where you say it is inevitable. That is pretty stark. That means it's going to happen.

Dr. GERBERDING. It will happen, I believe. I don't know when, and I don't know what virus will be the culprit. H5 is one possibility, but there are many other possibilities.

Senator SPECTER. All right. When you talk about inevitability, that's a good warning. That's not a shot across the bow; that's a shot into the ship. How serious will it be? Will it be like 1918? What's your professional judgment on that?

Dr. GERBERDING. My professional judgment is that I can't tell you, and I don't know, and I don't think anyone does. We've had a 1918 pandemic. That's probably not as bad as it could get. But we've also had very mild pandemics. For example, in 1957 it was not much different than a regular seasonal flu year, which is bad enough. Thirty-six thousand people die every year from regular flu.

Senator SPECTER. My red light is on and I will not go further. I would conclude with this comment. Don't wait for us to call hear-

ings. Call us. Don't wait for us to call you. We will call you with some regularity, as you've seen. But if something comes up, we want to know about it and you should tell us what needs to be done, because when you talk about a problem of this magnitude, we can attract the attention. We can push the key buttons if we have the information.

So let us know what Congress needs to do to respond, and you're going to have to undertake the job of quantifying, to the extent you can, the kinds of questions which I have asked. I'd like you to report back in 30 days, if you would, about what you can do in putting out information in a simplified form that can be transmitted to the public so they'll know how to respond.

Dr. GERBERDING. Thank you. May I just add one thing?

Senator SPECTER. Sure.

Dr. GERBERDING. There is a very important web site, pandemicflu.gov, and on that web site you can go to the information that individual citizens need. What we need to be able to do is get that out more generally, but we're making a start at what you're asking for and I'll be happy to provide you with some of the specifics.

Also, in a week or so we will be releasing an update on information that will describe better what communities need to do to protect their citizens at the local level if we have a pandemic with flu or some other virus. So there will be more information coming, and I'll make sure that you get it as it's available.

Senator SPECTER. Thank you very much.

Thank you, Mr. Chairman.

Senator HARKIN. Thanks, Senator Specter.

Senator Reed.

Senator REED. Thank you very much, Mr. Chairman, and thank you for your excellent testimony.

Dr. Parker and Dr. Gerberding, part of this national strategy involves the participation of States. Can you give us insight as to both their level of preparedness and the resources they're committing to this effort? Dr. Parker first.

Dr. PARKER. Well, first of all, it's just absolutely critical that individuals, localities, States, and that the Federal level have got huge responsibilities, and we have to be cognizant of the issue of complacency. We continue to take this threat very seriously and we're moving out aggressively on a number of fronts. But State preparedness is going to be absolutely critical to do the necessary planning and preparedness, and to include things like the antiviral procurements.

But most importantly, one of the things that we're going to need to be doing is exercising, testing the plans that are forthcoming and have come from the States. It's one thing to plan, have a written document, but it's a whole other thing that we exercise those plans, exercise those plans within a regional basis, and how those State and regional bases also function in a broader national response plan.

Senator REED. I appreciate your comments. I think they're exactly on target. But do you have an idea at this point of the level of preparedness? Alternatively, do you have a plan going forward to do these tests and the funding to do it? Third point, do you see

clearly, or let me ask directly, whose responsibility is it to generate these tests, evaluate the State response? Dr. Gerberding.

Dr. GERBERDING. It is CDC's responsibility to provide the leadership for that part of State preparedness, and certainly the network of public health is much broader than just CDC and the State and local health departments, because we've had to involve all of the important leaders at the community level.

When the flu summits occurred in every State, Secretary Leavitt brought together with the Governor the leaders of businesses and universities and churches and educational institutions and health care organizations and public health at the table, to really develop the network of planning that needs to happen to really penetrate all the different parts of society that would be affected by a pandemic. The Congress has appropriated $350 million in one supplemental to help States begin that process of planning and identifying what's missing. What do we need? Where are the gaps in people, the plans, the products, and the practice?

The next $250 million that they will be getting soon is specifically, primarily going to focus on practicing, and we have a curriculum of exercises that we will be expecting the States to conduct on their six key objectives, and sort of in a "crawl walk run," 18 different levels of activity that we will be monitoring their success in completing. We will be able to report to you at the end of that time, which will be many, many months from now, exactly who has achieved those objectives and who is still lagging behind. It's a process, but it is underway.

Senator REED. So in 18 months, for want of a better term, we can expect a report card from you on the capabilities of the States and localities?

Dr. GERBERDING. We hope that we will be able to provide more updated information than that. We're developing measurement tools, and we'd like to be able to have more regularized reporting of the status of our preparedness. But we are working on that now, and I'll be happy to make it available when we get the first draft of that.

Senator REED. Thank you. Just an observation, but one of the consistent problems at the State level, and I'll speak for my State, is the under funding of our public health agencies, not just with respect to this planning for pandemic flu but for a whole range of issues. They seem to be always towards the end of the line when there's issues of budgets at States and localities, and those issues obviously are with us again today.

Dr. GERBERDING. You are absolutely right. Part of the confusion I think people have about why aren't we more prepared as we should be, it's because we were in a very deep hole at the State and local level. People were starting from behind, and it's going to take a sustained investment over a long time to get us where we need to be in 2007.

Senator REED. Dr. Fauci, most commentators suggest that the arrival of avian flu will be inevitable, and the question is when. I wonder, does your research give us an idea of how much time we have to work through these issues?

Dr. FAUCI. I agree completely with Dr. Gerberding's assessment that it is really impossible to predict, Senator. You can't tell. We

don't even know, though we have some suggestions of what the molecular changes that would require something that is now extremely inefficiently going from chicken to human, and even less efficiently from human to human in the rare so-called clusters. We have some hints at the molecular level about what, if mutations occur, would make it more or less likely, but it's such a complex process that we just can't give you an answer.

We would love to say, "Well, there's a this percent chance," but it's impossible to do that. Which is the reason why, Senator, I emphasized with very predetermined purpose, the seasonal basis and the pandemic basis, because we can't tell you when the pandemic will be.

It may not even be an avian. It may be an H2N2 that people have already responded to, because the last time we had a problem with that was in 1957, so that as younger people enter the scene and older people die off, you may have a population that is naive to what is really a human variant. So when Dr. Gerberding and I and Dr. Treanor and Dr. Parker talked about pandemic, it doesn't necessarily have to be the bird flu. It's just something that has (*a*) never been seen before by the cohort that exists now and (*b*) that's quite virulent. That's how you get a pandemic.

So to just reemphasize what I was saying, if we take very seriously seasonal flu, all the ingredients that go into that, you know, people getting vaccinated more, having the production capacity, then we don't have to start from behind, as Dr. Gerberding said. We have a head start on it.

Senator REED. Well, thank you, Dr. Fauci. Just one final. My time has expired. Thank you. This is a follow-on to the issue of the State effort, and you mentioned it, Dr. Parker, about the antivirals.

Dr. PARKER. Yes.

Senator REED. We have made provisions to subsidize the acquisition, to also encourage States, but it seems that the take-up rate is very low relative to what we need. This would be, I assume, one of the first lines of defense if a pandemic strikes before——

Dr. PARKER. Actually I'll get the specific data State-by-State to you, but actually the information we have is that the take-up rate, at least the commitment to purchase, is actually quite high. In fact, upwards of or close to the total is already committed. Now, only 11 million has been purchased——

Senator REED. Right.

Dr. PARKER [continuing]. But there are at least commitments for the delta.

Senator REED. So we have goodwill but not product.

Dr. PARKER. That's correct. I think a lot of it, though, is dependent upon the availability, the right timing of the funding that the State will have, but at least there are commitments to purchase. But we'll get you a breakdown State-by-State so you can see the latest information and the latest data that we have.

Senator REED. Thank you.

Thank you, Mr. Chairman.

Senator HARKIN. Thank you.

Senator Durbin.

Senator DURBIN. Thank you, Mr. Chairman.

My question will betray my age. Last week I read a book by Bill Bryson about growing up in Des Moines, Iowa, in the 1950's, and he reminded me of my youth and of our fear of polio and our misunderstanding about what caused it, our knowledge that many children my age were afflicted by it with varying results, some extremely serious and some not so serious.

Then came that wondrous day when Jonas Salk, a name I had never heard before, became the savior for children across America, and Dr. Sabin as well, and we ran as quickly as we could to get this vaccine, knowing that we needed it, that we were exposed and needed that help. It may have created a mindset among people of my generation that you can work a miracle, that you can find this cure and somehow we can distribute it in time to save these lives. It's a very optimistic view of medical research. I hope it's realistic to some extent.

But as I listen to Dr. Gerberding speak about the three P's that she mentioned, I want to focus on the third one, people, and I want to ask this question: Do we have the capacity, do we have the people to do this basic research? Are people moving into the fields where we need them to move into, making a life commitment that they may need to make for us to find these cures, not just for pandemic flu but for many other things? I hope the answer is yes. If it isn't, I'd like to know what we could do to change it.

The second part of the question is, once we have found it, that vaccine, and I pray we will, do we have the capacity to distribute it in America at the level that we want to or need to? I think about our shortages of nurses and medical professionals. Last year in the State of Illinois we turned away 2,000 qualified applicants for nursing school, 2,000 qualified applicants, facing an overwhelming nursing shortage that we know is coming, because we don't have nursing faculty. We haven't invested in creating the faculty at these schools and the clinical opportunities.

So I want to go to the people issue and ask you, is that budding Jonas Salk in the wings, and many like him, many scientists and researchers like him? Once having found this vaccine, and I pray we will, do we have the capacity to distribute it, even in our own country, in an effective way?

Dr. FAUCI. Well, let me answer the people research component. There's also people health care delivery components, and I'll ask Dr. Gerberding to talk about the capacity of distribution.

At the NIH over the years we, with regard to training researchers, largely through the efforts of this committee and other committees, we have done very well. We've had a doubling from 1999 to 2003. At that time there was a great deal of enthusiasm about getting into the field of great opportunities, and we see and have seen researchers, young people who are getting in very excited about what they are doing, and we still have that. So this is not a complaint at all.

What happens, though, when you get into the vicissitudes that we have seen over the last couple of years, in which we have had flat budgets, has been a signal to the bright young people that maybe that's not the field necessarily that I want to go into. I don't think we're at a point of a crisis there in the sense that we've fallen back seriously, but I think we can't look at flat budgets when you

have research which by its very nature creates opportunity that begets more opportunity.

So the answer is, we have a lot of good people. I think we'll continue to get a lot of good people. We're doing a lot with the money we've gotten. But we've got to be careful that we don't send a signal to the bright young people about whether or not the opportunities are shrinking in this field.

Dr. GERBERDING. I have a somewhat less optimistic point of view about the work force at CDC. We are shrinking in our ability to be able to support our scientists. They've got wonderful space now, thanks to Congress, but we are not looking at an optimistic pipeline.

In part, in Federal Government there is the aging of the work force, and more than 20 percent of CDC's work force is eligible for retirement, so we have a very grave concern, and that is echoed throughout the State and local health agencies that are responsible for vaccine delivery and vaccine programs. So we are worried about the work force, and we are worried about it in many lanes, including the bench but also in the other public health sciences that are critical.

In terms of our ability to deliver a promising vaccine, I think we can handle that. We vaccinate the cohort of children every year who need all of their childhood vaccines, and that's a long list now, many appointments. So I think that we can build from what we know about immunizing children to develop a similar robust system for immunizing adults.

It will be much easier if we only have to do it once or twice. If we have to do the entire adult population every year, we need to change the way we think about adult immunization programs, and we've got some work to do on that.

Senator DURBIN. If I could ask one followup question, in the dismal world of budgets we are facing in 2 weeks this continuing resolution, and some have said that if we are not careful, that we could end up creating some serious problems in the commitments that have been made for research. Do you have any observation of what a continuing resolution at last year's number would mean to this effort in terms of research for a pandemic flu vaccine?

Dr. GERBERDING. I would say one of the flu-specific concerns we have is that our resources have come as supplements. That's one-time funding, and so you need a sustained engagement in order to be able to recruit and hire people into permanent career development opportunities.

So the good news is we have the supplement, and we're doing a lot with it and we're very excited about the progress that it has allowed us to accomplish, but it's that sustaining effort. You know, this isn't just we're preparing this year or next year. This is a long-term commitment for exactly the reason Dr. Fauci has emphasized, because with this investment we will save lives from seasonal flu. People don't need to die from influenza in the United States, but we have got to get this done and sustain the effort so that we can get into a polio-like situation instead of this ongoing tragedy that we have every year from seasonal flu.

Senator DURBIN. Thank you.

Dr. FAUCI. Senator, you asked the question about a continuing resolution, what it would do to, for example, the granting, the fundamental basic research grants. We fund by peer review, and we measure what we call a success rate, namely what is the percentage of people who put a grant in who get funded.

If we stay at a continuing—and these are just facts, numbers, this is not opinion—if you look at a continuing resolution at the current level, the success rate for our people who are putting in grants, new grants, young people getting excited, will be the lowest that I've seen it since I have been there. So those numbers just speak for themselves.

Senator DURBIN. Thank you.

Thank you, Mr. Chairman.

Senator HARKIN. Let me just say to my friend from Illinois that last year, as a result of hearings like this and beginning to look at what we needed for infrastructure in this country, it occurred to me, and I had my staff look at the expense of it, what it might cost to introduce legislation, which I will again soon, and I invite the Senator's participation in that, and that is to provide a free flu shot to every American every year, just free. Right now they are, what, $10, $15, $18, something like that, and most people go to a doctor's office or someplace like that.

But by providing a free flu shot for seasonal flu you accomplish a number of things. Aside from the 36,000 deaths every year, you'll cut down on a lot of lost work days that you won't have anymore, plus you build up the infrastructure. The idea was to find outlets where people could get free flu shots: Wal-Mart, grocery stores, churches, after church on Sunday here, that type of thing, to set up. That way you train people. You train a whole cadre of people in this country that know how to give a shot, and you have a structure set up, an infrastructure set up, so that if or when this pandemic hits, then you've got a system set up to distribute it and get people vaccinated in a hurry.

I forget the cost of it. I think it was, if I remember right, it was less than $1 billion a year. But when you factored in what you would save in terms of work days, unnecessary deaths, that kind of cost, it really dwindles into a very small amount of money. So I'm going to ask the panel a question, but to my way of thinking that was one way that we could start to move in that direction.

I don't know if you have any comments on that at all, any of the panel members, but the idea of giving a free flu shot to everybody in America, we have discussed this before. I don't know if you have any thoughts or anything beyond what I just said about it. If not, I'll move on.

Dr. PARKER. Before you move on, I really would like to emphasize the personnel and the expertise issue that you brought up just before. That is absolutely critical, and time and time again, having personnel and the scientific expertise, not only at the NIH and at the CDC but also I need to speak up for my colleagues at the FDA, to have the folks at the FDA that have the regulatory, the manufacturing experience. We need the scientific expertise in academia. We need the multidisciplinary expertise.

We have a strong bench right now. It is absolutely phenomenal working with all the scientists at the NIH and the CDC and aca-

demia and FDA. But I'm not sure we have a deep bench. I'm very concerned about that.

Senator HARKIN. I think, if I remember, on the polio shots, I think they were free. I think when kids got polio shots, I remember when we got our shot, I don't think we were charged for those. I don't know. I'm going to find out about that.

Dr. GERBERDING. They were free. I remember standing in line and getting it.

Senator HARKIN. They were free. There you go. They were free. Yes, Dr. Treanor.

Dr. TREANOR. I would just point out that the free flu shot idea, which I think is a really good one, would also provide a platform that could greatly facilitate the delivery of other important vaccines, and that would be a real advantage.

Senator HARKIN. Not just flu, it could be other things, too. You would start building up the system. Smallpox, yes, other things like that. Thanks very much, sir.

Well, I wanted to ask a question before we leave, a couple or three. I understand there are some trials on universal vaccines going on in Europe right now.

Dr. FAUCI. Yes.

Senator HARKIN. What do we know about that?

Dr. FAUCI. Well, they have started. Again, they are inducing an immune response. They appear to be safe. We can't say. They are too early, Senator. I mean, we always get that question. When a trial starts, they want to know how they're going. The trials are going well.

The question is, we don't have the answers yet as to whether or not it's going to be effective. We have animal studies that have looked really good, where you use the principle, the concept of for example an M protein in an animal, and you challenge the animal and you get good protection. But you've always got to be careful when you try and directly extrapolate, for example, a mouse study to a human. But thus far everything we've seen looks like it's on track.

Senator HARKIN. All this talk about a pandemic, can you give us some idea, how soon will it happen? I mean, if it happens, what kind of warning will we have? How rapidly will it spread? How much time will we have? Is this something that is going to flow through the populace in a matter of days, weeks, months? What's your best analysis of that? What kind of warning would we have? How much time would we have?

Dr. GERBERDING. It depends. The short answer is, we don't know, and the things that are most likely to influence that are where does it emerge. If it emerges in Atlanta, we'll probably know it fairly soon, but if it emerges in one of those countries that we haven't been able to support or invest or engage, then we're in trouble.

It may emerge slowly. It may gradually move from being in one species, chickens or pigs, for example, and then evolve gradually to adapt to humans, and we'll have time to recognize it and try to quench it before it goes too far. Or it may happen like SARS, where literally overnight that virus moved from a hotel in Hong Kong to the rest of the globe. We don't know, and we have to be prepared for the worst.

Senator HARKIN. But you were very successful on the SARS. You were very successful in containing that.

Dr. GERBERDING. In retrospect, we were I believe partially successful and partially fortunate. But we had a virus in that case that actually wasn't very transmissible unless you were very ill, and flu is not like that. Flu is sometimes transmissible before you even know you have it.

Senator HARKIN. Right.

Dr. GERBERDING. So it's a much different risk, and we think a much higher risk.

Senator HARKIN. Because the scenarios I've read about, heard about but mostly read about, is that a traveler goes to one of these countries, you pick up this flu strain. You get on a plane. You're in a closed environment. You don't know you have it. It gets circulated in the airplane. Others may pick it up. You come back to the States. You go to your community, and bit by bit all of a sudden it just starts to spread almost in a geometric fashion.

Dr. GERBERDING. There are several things that we're doing to rehearse for that situation. One of them, thanks to our appropriation, we have been able to now have 20 quarantine stations at major airports around the country that would be dealing with those planes full of passengers but also a number of other activities to try to protect our country from introduction.

But also we are working on the ability to rapidly diagnose a new strain, not in a laboratory but at the bedside or wherever the first point of contact with an individual who is suspicious for illness, so that we can speed up our recognition and then the quarantine that would be necessary to isolate that person and protect others. So there are a lot of scenarios like the one you've described.

I think it's fair to point out, however, that many people believe the 1918 pandemic started in the United States, so it's not just about something over there. We're all in this global network together, and it could happen anywhere.

Senator HARKIN. Dr. Fauci.

Dr. FAUCI. Just to amplify very briefly on everything that Dr. Gerberding said, ditto to everything she said, but we get uncomfortable when we get asked questions by people like you who we know, we've been dealing with so long. "Why don't you have a precise answer for us?" is what you're probably saying to yourself.

Senator HARKIN. I'm only asking you the questions my constituents ask me.

Dr. FAUCI. We appreciate that, but the issue, in addition to everything that Dr. Gerberding said, is that there are many variables to this. You're asking a precise question, and in order to give an answer you have to put all the variables in. I'll give you two of those variables.

One, that Dr. Gerberding alluded to, we're talking about, let's take H5N1, and it may not even be H5N1, is that the evolution to go efficiently from human-to-human as efficiently as the seasonal flu goes is a big, big spectrum. It could start to go human-to-human but very, very inefficiently. That will have enormous impact on how long it takes to develop the efficiency, if it ever does. So it can go from extremely inefficient to very, very efficient but there's a wide

spectrum. That completely impacts all of the questions you ask about speed.

The other question that is very closely related to that is, how devastating would it be? You have again, within what we already know about pandemics, a big spectrum. You have the 1918 pandemic with more than 50 million people killed, and then you get 1968 which, although it's officially categorized as a pandemic, was not historically significantly different than what you actually see with a seasonal pandemic.

So you have these crossover, confounding variables which make it very, very difficult to give a precise answer to the question. We don't want to give a precise answer if we don't have the science to back it, because it will come back to bite us and it will come back to bite you.

Dr. GERBERDING. It's like preparing for a hurricane. You know they will occur but you just can't say when, where, how bad, or who will be affected.

Senator HARKIN. Fair enough, but you do know that hurricanes hit the coast. They don't hit Iowa.

Dr. GERBERDING. Yet.

Senator HARKIN. You know basically where they're going to hit, so you can kind of plan for that. You know how buildings, we know from history building codes and how you build and how you plan for things like that. So there are a lot of things we can do to mitigate the damage done by hurricanes.

Well, we've got a lot of historical analysis here on medicine and pandemics. We've had them before. We know basically how they spread, the mechanisms thereof.

Now, I understand that you can have one hurricane hit that's 70 miles an hour wind, and then you can have another one that's 150 mile an hour wind, so you can't plan for everything. But there are certain basics that you can do, and that is to set up an infrastructure so that you can take care of the mild to the strong. You can do research and find out what are the best buildings that you can build and how you build them safely. In this case it's the vaccines and the adjuvants and the antivirals that we have.

Dr. FAUCI. That's what we're doing, right.

Senator HARKIN. I don't mean to take this analogy beyond any reasonable comparisons, but it would seem to me that—I know you can't say precisely, but within that broad spectrum, what can we do to make sure that we respond to the needs of our society, to prepare for it?

Now, the reason I asked about the time frame has to do with vaccines. I am told that from the outbreak of a pandemic or something like this, it might take 4 months, 6 months to develop the vaccine once you isolate the virus, develop the vaccine.

Well, again, we're putting money into these building blocks, into research on vaccines. Egg-based, we know that. That seems to be a well understood science. Then there's cell-based, which is maybe not quite so well understood. I don't know. You can correct me on that. But we have put money into cell-based, which they tell me would be a shorted period of time than egg-based production.

Then I have people come to my office last year telling me about RNA vaccine, and then there's something called a synthetic vac-

cine. They're all telling me the time gets shorter and shorter and shorter to be able to isolate the virus and develop that kind of vaccine.

Well, I mean, this all gets rather confusing after a while. So from our standpoint, from a public policy standpoint, what should we be doing in terms of developing or helping you all develop these other systems? Is an RNA-based system the way we ought to go because it would be so rapid? Will it have more applicability to various strains that may come up, rather than an egg-based? So that's why I ask you, how much time do we have?

Dr. FAUCI. Well, your question is a great question, and I can tell you very briefly that what you're talking about was the second bullet on one of my slides, with the development now of alternative platforms, we call them, or alternative vaccine candidate types, a DNA vaccine, a vector vaccine, all of those. Number two, develop novel vaccine approaches.

So we're doing that now. I can't answer your question of when we're going to get a pandemic, but I can answer number two. I can tell you that no matter what happens, we are going to assume—and that I think answers the question that was implied in your statement—we are assuming that the worst is going to happen. Not only that, we're assuming that the science and the public health preparedness—now, if you do that in a vacuum, Senator, and it doesn't happen, you are very, very open to the justifiable criticism that it was a scare tactic and what you did is, you got everybody exercised about it and nothing happened.

That's the reason why we're all linking it to seasonal influenza, because a DNA vaccine, a vector vaccine, a vaccine that is grown in cells, a vaccine that you could turn over in 2 months instead of 6 months, all of that is going to help the seasonal flu. Developing the capacity to be able to make hundreds of millions of doses as opposed to trying to squeeze it out, as we've had to do for the past few years, will happen if we're treating seasonal influenza in a way in which we're getting as many people who should be vaccinated, vaccinated.

The CDC, and Julie can speak to that much better than I, have been going in that direction for the past several years. So even though we can't give you an answer precisely when, we are acting like we're going there by what we're doing from a research and a preparatory standpoint. Julie?

Dr. GERBERDING. I think one thing to remember is that our science is better now. We do have much better global detection capability than we even had a decade ago. So if something emerges, our ability to know it sooner is certainly a major step forward to us, and it allows us to have a more rapid time frame between the virus appears and we have the vaccine.

But it's not short enough to save all of the lives that we will be accountable for, and that's why all the other building blocks, just like—again, not to dwell on the hurricane analogy, but we're doing all of those things. We're doing things that would harden communities. We've got to do more to build the capacity to take care of sick people. We need more studies of how to use antivirals. We need more antivirals.

We need a whole lot of things that are the building blocks of preparedness. Even though we can't say exactly when we would need to use them, we believe we will be using them, and these investments that we're making now are a big part of that but we've got a long way to go. I think we're kind of giving a mixed message here because that's the situation we're in. We've made a lot of progress but we all are sobered by the unpredictability of the problem and the number of steps that we have to go before we've really got the job done that we feel would be the optimal preparedness.

Senator HARKIN. I guess what we need to do here on this committee is to, again with the help of our staff and contacting your staff, you know, we've put all this money into it, how much was it, now? $6.1 billion, but some of that was for State and local preparedness, about $600 million, so we're $5.6 billion. So that's somewhat less than the $7.1 billion that we initially requested.

I think what we need to get a better handle on is. We started all this stuff last year, developing more vaccine supply, to do more research I guess into adjuvants. I guess we need to know where are we on that road, and do we need to do anything more this year to enhance that, or are we okay where we are, or have we been lulled a little bit?

I think that's where we started this whole hearing off. We've been sort of lulled into a sense of complacency. Is what we did last year fine, we don't have to worry about anything, or is there something else happening that we need to pay attention to again this year in our next budget cycle? That's really what we're groping for here. That's what we're trying to find out. Or are we just fine and we can coast for a couple of years?

Dr. FAUCI. I don't think we could ever say fine. Whenever you're dealing with a threat to the public health and you're dealing with trying to push research, push public health, push infrastructure maximally, we never accept that we're fine. We could always do better and we could always do more.

But the feeling of complacency is not what's going on in the preparedness. For example, the last thing you just mentioned, the Secretary just signed contracts to $132.5 million, just a little while ago, a few days ago, on the adjuvant dose-sparing technologies for three separate companies, one of which has a novel way of using a patch component to make an adjuvant essentially be easily administered.

So these things are going on. You may not be hearing about it. The things that we spoke about at the hearing last year, and we said this is about to happen, they're happening now. The clinical trials that I promised you would go on, Dr. Treanor and his colleagues are already implementing many of them, so things are happening. Can we do better? Can we do more? Can we use more resources? Of course.

Dr. PARKER. I think it's really a multipronged approach here. That is, we have to go with the technology that's available today. We have harnessed actually a lot of the information that has already been invested in, say for the cell-based approach, and we're continuing the basic discovery so we can get to reliable, scalable, rapid vaccine candidates and platforms that we need.

So the infrastructure and the investments we're making today are also looking with an eye to what's going to be coming out of the research base, and we're not, as Dr. Fauci said, we don't suffer the complacency internally. We will work with you to see how we can better do that communication on the risk assessment.

But I would also like to perhaps invite—sometime perhaps our collective staffs can come over and give you a little bit more detail on that multipronged approach, when we have more time to go into more depth, and I'd be glad to do that.

Senator HARKIN. We'll follow up with you on that.

Okay, from the broad, we started with the narrow on bird flu, broad, and now let's come back to the narrow on the bird flu itself. That's what gained a lot of attention last year, and still does periodically, not as much. But as you point out, Dr. Gerberding, over 50 percent of the people who get it die.

My question on bird flu has to do with this. Is it, is the mortality rate the same among all age groups? Is it older people get it? Is it younger people? What kind of data? We've had, what, 3 or 4 years now of looking at this and examining the people who got it and have died. What do we know about it? I forget the word, but what do we know about how that operates among various age groups?

Dr. GERBERDING. The major determinant of who is getting it probably has to do with who has contact with birds in the family environment.

Senator HARKIN. There's no difference on age? If young people have contact, they——

Dr. GERBERDING. Exactly, so young children and young adults are probably disproportionately affected because they're the most likely to be either playing with chickens or handling chickens that are being tended by family members. There does not seem to be much difference in mortality once you get it. It is so fatal that, you know, whether you're a young, healthy child or not, you still have a greater than 50 percent chance of dying.

Senator HARKIN. Now last year Senator Stevens, I know, was talking about this, about the Alaskan flyway. We saw data where this was spreading up into Japan, Siberia, up that way, and he thought, well, the birds will be flying across there and bringing it down in the United States. Is our surveillance very good? I mean, nothing has come. We've not picked up one yet in the United States. Is our surveillance good enough to pick up something right away?

Dr. GERBERDING. We've made amazing progress in the United States. The Geological Survey and the USDA scientists have created a sentinel system where they're screening wild birds and also any domestic bird in a commercial flock who dies. There's a complicated surveillance system already in place for them. They are including, obviously, H5 screening in that assay.

I don't think any of us would say that a bird is not going to sneak through the cracks and get into the United States. That would be naive, given the tremendous movement of migratory birds. But it's also important to remember that birds move other than by flying. Sometimes they are traded as live animals, and we have restrictions on that in the United States but not all countries

do. Sometimes birds are smuggled, and they can be smuggled for a variety of reasons, but some of the species of birds that are popular smuggling targets can harbor H5 viruses.

So we've got to be concerned with the movement that people induce, and of course the worst case is that someone could do something like this intentionally, and that is also one of the things that we have to always keep in mind. So while we've got one system that has drastically improved in the last year, and we are certainly working aggressively at the borders for any importation, there are numerous ways of spreading and we have to be alert to all of them.

Senator HARKIN. Wasn't the 1918 virus, didn't they finally figure out, wasn't that also a bird virus?

Dr. GERBERDING. We have worked with our collaborators in the Department of Defense to characterize the 1918 virus, and it has the signatures that strongly indicate it was an avian origin. Where it merged from birds to humans, we don't know, and there is more work going on with more constructs of that virus that might give us additional clues.

The last two pandemics were not avian viruses. They were caused by a reassorted virus, where a seasonal flu virus mixed, probably in a pig, with another flu virus and genes were exchanged, and that's where the H2 and the H3 emerged. So it can occur either by evolution from bird viruses or by mixing up human genes, and again we can't say which is the most likely.

In an area of the world like Asia, where there is an intense mixture of pigs, poultry, and people—I guess I'm saying a lot of P's today—but poultry and people, you just have an incubator where the mixing and matching of these flu virus genes is at its best, and so there are certainly areas of the world where are differentially investing our resources for surveillance because we believe that would make sense. It's like putting your hurricane preparedness along the coast. There are areas where just biologically this could be more likely, and we want to make sure we have the strongest systems for detection and response in those areas.

Senator HARKIN. Before I close up, Dr. Treanor, do you have anything you want to add to enlighten us in our search for what we should be doing this year and what we need to be focusing on?

Dr. TREANOR. Everything has really already been covered. I will point out that it is critical to maintain, I think, the very excellent portfolio that Dr. Fauci has mentioned of investigator-initiated research through traditional granting mechanisms, to maintain that fundamental base of basic science that supports all of these activities, and I think that's important not to forget about as these funding decisions are made.

Senator HARKIN. Anything else, before we move on?

Well, I guess I would just maybe try to sum it up by saying that the threat that made the headlines here within the last couple of years and got everyone alarmed, and now has subsided, the threat is still as real if not more real than it was then; that in the last year we have made some progress. We have begun funding the development of vaccines, and we're doing more research into the other methodologies of developing those vaccines.

We are beginning to stockpile antivirals. Well, now, maybe I should have talked about that. Our goal was—what was it? Twen-

ty-five percent. We had a goal of 25 percent, a stockpile of antivirals that would reach 25 percent of our population. I don't know where we are right now. Where are we on that?

Dr. PARKER. We're right on target. We're right on target with our plan, with the funding available, where we're at right now, and I've got the numbers in my testimony. But we're on target with the plan, and a lot of this is going to come to completion by fiscal year 2008.

You know, another thing that is I think an important part to comment on, too, with the antivirals, some of the programs particularly with antivirals also stimulate the industry to move in a positive direction as well. The programs were successful in that regard in establishing a capability, an increased capacity to manufacture antivirals, so that has been I think a very positive, another positive aspect of these programs.

Senator HARKIN. So we're on target on the stockpile?

Dr. PARKER. As far as the planned, our plan to purchase, to date.

Senator HARKIN. Well, maybe we need to, again, take another look at that and see if that should be ramped up or what. I don't know. We'll have to take a look at that this year.

Also I think it seems to me the one place where we are falling down or inadequate is in developing systems to get vaccinations out to people in a short amount of time and having the State, local governmental agencies, public health agencies, but also other entities structured in a way that we could respond to this.

I mean, we can have all the antivirals we want. We can get great vaccinations ready, and the pandemic hits, and all of a sudden, who is out there to administer it? What's your structure? How do you deliver it? How do you inform people?

It seems to me that's the one place, at least from my limited knowledge, where we're kind of falling down on this. It seems the research is moving ahead fine, the CDC is doing its job, our researchers. The drug companies are developing these, they're looking at them, but we're not developing that infrastructure.

Dr. GERBERDING. I agree with you, and I want to emphasize that one of the requirements for the States' money is to exercise a plan, and this year they were expected to exercise their vaccine delivery capability using seasonal flu vaccine. So we're practicing at the State and local level.

In Iowa, 100 percent of the health districts in the State, the county health departments in the State, have plans. But now coming up we'll be asking for more formalized exercises to understand where the gaps really are, and if we believe there's a systems problem here, what is it and what else is necessary to fix it? So I think after these exercises develop, we could give you more information about what gaps appear to be present and what we think needs to be done to close them.

Senator HARKIN. That's encouraging. That's going on right now?

Dr. GERBERDING. Yes, it is.

Senator HARKIN. Nationwide, or just sort of——

Dr. GERBERDING. In every State, in 62 jurisdictions, the States, the territories, and in four cities in America that we fund.

Senator HARKIN. So you'll have some data on that, what, by this summer or something like that?

Dr. GERBERDING. Yes, we will.

Senator HARKIN. Well, that would be okay. That would be okay. We won't be done with our budget and our appropriations by then, will we? That would be very helpful, because I just sense that we've really got to focus more in that area.

CONCLUSION OF HEARING

Well, if there's nothing else, I want to thank you all for not only being here this morning, but each one of you, thank you for your leadership in this area and so many other areas of biomedical research and surveillance and public health. Thank you all very much.

[Whereupon, at 11:30 a.m., Wednesday, January 24, the hearing was concluded, and the subcommittee was recessed, to reconvene subject to the call of the Chair.]

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