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COMBATING THE FLU: KEEPING SENIORS ALIVE

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BEFORE THE

SPECIAL COMMITTEE ON AGING
UNITED STATES SENATE

ONE HUNDRED EIGHTH CONGRESS

SECOND SESSION

WASHINGTON, DC

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COMBATING THE FLU: KEEPING SENIORS ALIVE

TUESDAY, SEPTEMBER 28, 2004

U.S. SENATE,
SPECIAL COMMITTEE ON AGING,
Washington, DC.

The committee met, pursuant to notice, at 10:04 a.m., in room SD–628, Dirksen Senate Office Building, Hon. Larry E. Craig (chairman of the committee) presiding.

Present: Senators Craig, Bayh, and Carper.

OPENING STATEMENT OF SENATOR LARRY E. CRAIG, CHAIRMAN

The CHAIRMAN. Good morning, everyone, and welcome to today's hearing, which deals with an especially appropriate topic, as we find ourselves in the first days of the National Adult Immunization Awareness Week. This year's theme is building a path for a healthier tomorrow. I suppose we could say that we are here this morning to find out how that path is being built and where it leads, and just how safe is that path for today's older Americans?

Last year's vaccine shortages combined with an unusually early flu season resulted in heightened awareness of the importance of immunization. With news reports of people standing in line for hours to be immunized, many of us questioned for the first time whether we can assume that everyone who needs a vaccine can obtain one.

Today's hearing will focus on adjustments that have been made to the public health system as a result of last year's challenges. We will hear testimony as to what announced delay in production might mean for the flu season and the implications for America's seniors as we move forward in pandemic preparedness planning.

I realize that flu does not limit its attacks to the aging population exclusively. However, this potential killer certainly poses a high risk for this country's seniors. Last year, 36,000 Americans died from exposure to flu. Approximately 90 percent of them were over age 65. I think there are those in the community who say this is a killer of our old.

In my own state of Idaho, with the exception of one victim, all of those who died were over the age of 50. Another 200,000 people were hospitalized across the country. Influenza is a serious disease. We cannot underestimate the danger it poses to the seniors of today and the boomers of tomorrow.

Because of this concern for our citizens, I joined with Senator Bayh, who I think will be with us in a few moments, and who cer-

tainly was instrumental in encouraging this hearing today, I joined with him in introducing Senate 2038, the Flu Protection Act of 2004. I look forward to hearing how elements of this legislation are currently being addressed in the public health system and by vaccine manufacturers.

We are pleased to be joined today by experienced public health officers or officials including one from my home state of Idaho and the Government Accounting Office. We are also joined by the President and CEO of one of the few manufacturers who continue to provide vaccines in the United States.

I believe many of you here are particularly interested in hearing more about the announcement their company made earlier this morning on the topic.

We have two panels this morning. On our first panel we will have Dr. Ostroff, deputy director for the National Center for Infectious Disease at the Center for Disease Control and Prevention. We will have also Dr. Pamela McInnes, deputy director of the Division of Microbiology and Infectious Diseases at the National Institute of Allergy and Infectious Diseases.

Our second panel, we will hear from Janet Heinrich, director of Healthcare and Public Health Issues at the Government Accounting Office. She will be joined with a consultant from my home state, or constituent I should say from my home state, Carol Moehrle, district director of the North Central District Health Department, located in Lewiston, ID. Finally, we will have Dr. Howard Pien, CEO and president of Chiron Corporation.

We want to welcome all of you this morning for taking the time to be with us. I think you have an important and valuable message to America and especially to America's seniors. So with that, Dr. Ostroff, we will start with you.

STATEMENT OF STEPHEN M. OSTROFF, M.D., DEPUTY DIRECTOR, NATIONAL CENTER FOR INFECTIOUS DISEASES, CENTERS FOR DISEASE CONTROL AND PREVENTION, WASHINGTON, DC;

ACCOMPANIED BY LANCE RODEWALD, DIRECTOR, IMMUNIZATION SERVICES DIVISION, NATIONAL IMMUNIZATION PROGRAM, CENTERS FOR DISEASE CONTROL AND PREVENTION

Dr. OSTROFF. Thank you very much, Mr. Chairman, and let me thank you and this committee for their leadership on this and many other important public health issues. Let me also introduce Lance Rodewald, who is the director of our Immunization Services Division in the National Immunization Program, who will be here to answer questions.

The CHAIRMAN. Lance, welcome to the committee.

Dr. RODEWALD. Thank you.

Dr. OSTROFF. Let me begin by thanking you for a very timely hearing since we are now entering the new influenza season. Many of our public health issues particularly strike older Americans, and therefore we look forward to working jointly with you to find solutions that impact this population. This is especially true for flu.

CDC analysts, as you pointed out, recently published a report in the Journal of the American Medical Association updating data on

the burden of influenza as measured by hospitalizations in the United States. This analysis unfortunately revised upward the annual number of hospitalizations to 200,000.

As you mentioned, in addition we estimate that 36,000 Americans die each year from the flu, and this is just during an average flu year. The seeds of this bad news lie in the otherwise good news that today Americans live longer. Fully, 90 percent of deaths from complications of the flu occur in persons over the age of 65 years, as do about two-thirds of those hospitalizations.

Therefore, as Americans live into their eighties, nineties, and even reach the century mark, the number of persons at highest risk for severe consequences of the flu rises too. Far too many of these hospitalizations and deaths are avoidable, even those that occur among our oldest citizens.

The keys to prevention when it comes to flu are vaccination, vaccination, and vaccination. Let me explain. First, all senior citizens should be vaccinated against the flu. This vaccine clearly reduces the chance someone will get the flu. Even if they do get the flu, their chances of having serious complications are much, much lower.

Second, we need to make sure that older Americans get other vaccines that work in concert with the flu. This is especially true of the pneumococcal vaccine which many people commonly refer to as the pneumonia vaccine.

Third, we need to make sure that the people who spend time around older Americans during flu season are themselves vaccinated. When such persons themselves do not get the flu, they cannot spread it to others who are around them. That is why we target those who share the same household with, and those who provide services to, older Americans.

When it comes to flu vaccine, the news is often good and bad at the same time. As you can see on the poster here, without question, we have made steady progress in getting flu vaccine to persons over the age of 65. Today, about two-thirds of these persons get an annual flu vaccine, but that also means that about a third of them do not, and that we have a ways to go to reach our Healthy People 2010 goal of 90 percent.

We also see a clear equity gap. African American and Hispanic seniors are far less likely to be vaccinated against flu than are the others. As for healthcare providers who are not shown on this graph, our surveys show us that only about one in three get an annual flu shot. So clearly, we have our work cut out for us.

As you know, last season was especially difficult. First, it came on more rapidly and earlier than almost any recent flu season. Second, several locations suffered from a series of very highly publicized and tragic deaths in young children. Third, there was rising concern about avian influenza, or bird flu, in Asia.

These factors drove an unprecedented demand for flu vaccine, a demand that could not be met, resulting in a run on remaining vaccine and coast-to-coast shortages.

Unfortunately, last season came on the heels of several years of fairly mild flu activity. As a result, as seen here on this graph, in those years, vaccine supplies began to far exceed demand and many doses went unused and had to be unfortunately thrown out.

So in 2003, the two primary domestic manufacturers cut back their production to balance the supply with the demand. At CDC, we have been working to reduce the chance of a similar problem this year.

First, we have improved our surveillance. In addition to having better monitoring systems for flu itself, we are now working closely with the manufacturers and distributors to better monitor the vaccine supply. This way we can be more certain we know how much is out there, where it is, and can anticipate problems, and we have created a buffer stockpile of 4.5 million doses should any shortages arise.

The manufacturers have also responded by increasing production to a record 100 million doses. As a result, the potential for similar problems this season is much lower. But more needs to be done. We would like to see more people get vaccinated against the flu.

Shown here are some of the posters we have used in this year's educational activity. This one targeting seniors and the next poster targeting healthcare workers. Meeting our goals will require work on all of our parts: policymakers, public health, the health care system, and industry.

This is why for the past few years, we have been working through a coalition known as the Influenza Summit. We have also partnered with CMS on a project to allow standing orders for flu vaccine.

Before closing, let me just touch quickly on more issue which is pandemic flu. Given the ongoing problems in Asia, many believe today we are closer to the next influenza pandemic than we have been in decades. These strains in Asia have already demonstrated two of three requirements for a pandemic.

First, there are flu strains that have not been widely circulating in humans, and second, they produce very high fatality rates. All they now need to do is acquire the ability to easily spread from person to person. HHS has been taking steps to address this threat. We have expanded our monitoring systems in Asia and with WHO. We have assured year-round egg availability for vaccine production. We are stockpiling antiviral drugs, and we are developing and purchasing pilot lots of vaccines against the strains of most concern. In August, we published the draft HHS Pandemic Plan which is now undergoing a 60-day comment period.

So, in summary, flu has been and will remain a very serious concern to the health and well-being of all Americans but especially older Americans. We look forward to working with the committee and with Congress to meet this challenge.

Thank you very much and we will be happy to take questions.

[The prepared statement of Dr. Ostroff follows:]

Testimony
Before the Special Committee on Aging
United States Senate

Combating the Flu: Keeping Seniors Alive

Statement of
Stephen Ostroff, M.D.
Deputy Director,
National Center for Infectious Disease
Centers for Disease Control and Prevention
U.S. Department of Health and Human Services

For Release on Delivery
Expected at 10:00AM
Tuesday, September 28, 2004

Good Morning, Mr. Chairman and Members of the Committee. I am Dr. Stephen Ostroff, Deputy Director, National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC). I am accompanied today by Dr. Lance Rodewald, Director, Immunization Services Division of CDC's National Immunization Program. Thank you for inviting us to provide information on the upcoming influenza season, especially with regard to older Americans. CDC has been working hard for many years to raise awareness of the need for influenza vaccinations, and we appreciate your interest in and support for preparedness for this and future influenza seasons.

Introduction

You may have heard of the recent CDC study published in the Journal of the American Medical Association showing new estimates that more than 200,000 respiratory and circulatory hospitalizations and 36,000 deaths are associated with influenza each year in the United States, substantially more than previous estimates. The report notes that the aging of our population is an important contributor to the increasing numbers of influenza-associated hospitalizations and deaths. Based on US census estimates, the numbers of very elderly people (85 years and older) in the United States will continue to increase. Consequently, the numbers of influenza-associated hospitalizations and deaths will also likely increase over time unless we take action to strengthen our vaccination efforts. According to the National Health Interview Survey, only about 64 percent of those over age 65 were immunized for influenza in 2002. Although this is a higher percentage of influenza vaccination than for other targeted groups, it is still insufficient. Additional efforts are needed to ensure that current recommendations for influenza vaccination for all high-risk individuals, those who

live in households with high-risk individuals and health care workers that care for these persons are fully implemented. Efforts to vaccinate older Americans and their contacts annually must continue to be a priority for immunization programs.

The elderly population is steadily increasing worldwide due to improved healthcare practices and advances in medical science. However, illnesses caused by a number of infectious diseases are still high when compared with that of younger individuals. This is due to a decline in immune function, which affects both the ability to resist infectious diseases and the ability to generate protective immune responses following vaccination. As a result, the incidence of severe respiratory disease, not only due to influenza but also due to respiratory syncytial virus (RSV) and pneumococcal pneumonia, increases in the elderly.

Surveillance and Vaccine Strain Selection

Protecting individuals who are at greatest risk of serious complications from influenza through vaccination is the primary strategy for preventing severe complications from the disease, including associated deaths. CDC, in collaboration with WHO, FDA, and regulatory agencies from Australia, Japan, and the United Kingdom, examines data to determine what, if any, vaccine strain changes should occur each year to keep the vaccine well matched with the currently circulating influenza strains. We know the vaccine works best when the vaccine strains are closely matched to the strains that circulate. As part of the vaccine strain selection process each year, CDC studies the immune response of vaccinated volunteers to determine how well the current vaccine protects against the currently circulating influenza viruses. Responses in young children, healthy adults, and older persons are examined to help ensure that the vaccine

strains selected are the best overall choice after taking all age groups into consideration.

Although we cannot predict the timing or severity of the influenza season, we are constantly monitoring influenza viruses worldwide for changes that might indicate the need to change the vaccine strain. So far this season, very few influenza viruses have been isolated from U.S. patients. However, the majority of strains that CDC has characterized are well matched to the vaccine that has been produced for the coming season.

Influenza Vaccine Supply: Past, Present and Future

U.S.-licensed influenza vaccine is produced by three manufacturers, two making inactivated vaccine and one making a live attenuated vaccine delivered by nasal spray. All vaccine is produced, and the vast majority distributed and administered, by the private sector. Because of the time required to manufacture vaccine and the need to obtain adequate supplies of embryonated eggs in which influenza virus is grown for vaccine production, manufacturers must predict demand and decide on the number of vaccine doses to produce 6 to 9 months before the onset of the influenza season.

Production of vaccine for the 2003-2004 influenza season was based on the previous year's demand. During the 2002-2003 influenza season, supply exceeded demand by approximately 12 million doses, which were not sold. Therefore, the next year manufacturers produced about 83 million doses of the inactivated vaccine, as well as about 4 million doses of the live attenuated vaccine, for a total of approximately 87 million vaccine doses. Unfortunately,

last year the demand for influenza vaccine in the United States exceeded what had been experienced in previous influenza seasons. We believe this shortage resulted from the early onset of the influenza season, which occurred during the months that vaccination usually takes place, and the widespread media reports of influenza-caused deaths among children.

Based on information from influenza vaccine manufacturers, 100 million doses of influenza vaccine will be available to Americans in 2004. This record number of doses should be an adequate supply for the upcoming season. However, demand is always difficult to gauge, and this year influenza vaccination is being recommended for the first time for all children 6 months to 23 months of age by CDC, the American Academy of Pediatrics, and the American Academy of Family Physicians. In an attempt to foresee a shortage, CDC conducts weekly calls with influenza vaccine manufacturers to monitor vaccine supply throughout the influenza season.

In addition, in August, one of the two manufacturers of inactivated influenza vaccine announced that some vaccine lots, amounting to approximately 2 million doses of vaccine, were contaminated and cannot be used. The manufacturer is retesting the remaining lots of vaccine for sterility, and this additional testing will introduce a delay in the release their vaccine by approximately one month.

On the plus side, CDC has contracted for the first time ever for a stockpile of inactivated influenza vaccine (4.5 million doses) for the upcoming season. This vaccine will become available early in December 2004. This stockpile should work to cushion any concerns about potential shortfalls.

DHHS is currently working on long-range strategies to improve future influenza vaccine supplies. The current egg-based system used to produce licensed influenza vaccines – despite being reliable for more than 50 years – can be improved. Challenges to the current system include: 1) a lengthy manufacturing process; 2) the need to select which virus strains will be in the vaccine at least six months in advance of the influenza season; and 3) the need to produce 100 million plus doses of a new influenza vaccine each year, the amount needed to vaccinate all at risk people. The current production techniques cannot be scaled up rapidly enough to provide additional doses of vaccine if demand outpaces supply in a regular influenza season. Despite these challenges, egg based vaccines will continue to play an important role in the supply of influenza vaccines. To address the issues presented by current technology, DHHS is encouraging the development and U.S. licensure of influenza vaccines produced with new technology, including the development of cell culture-based vaccines. Resources have been made available in the FY 2004 budget, and requested in the FY 2005 budget, for this important activity.

Influenza Vaccine Recommendations and Improved Vaccine Coverage

Each year, CDC works with the Advisory Committee on Immunization Practices (ACIP) to review and update influenza vaccination recommendations. Relevant highlights of these recommendations include annual influenza vaccinations for all individuals 50 years of age and older, for individuals with medical indications including chronic diseases, such as cardiovascular disease, asthma, diabetes, and immunosuppression whether caused by medication or disease regardless of age, as well as for all persons in long term care facilities. Children between 6

and 23 months of age and close contacts of high-risk individuals should also get vaccinated.

Workers in certain occupations, who are likely to transmit influenza to others, should be vaccinated. This is especially true of health care providers. According to the National Health Interview Survey for Health Care Workers, only 38 percent of health care providers in this country receive influenza vaccine annually.

These annual ACIP recommendations are published before each influenza season so that providers can become familiar with them and have time to implement any recommended changes. Through our educational efforts for providers and the public, we are stimulating increased demand for vaccine. To achieve our Healthy People 2010 targets of vaccinating 90 percent of adults 65 years and older and 60 percent of high-risk adults ages 18 to 64, we will need to increase these efforts and address other barriers to vaccination. CDC and its partners are working in many ways to improve influenza vaccine uptake.

1. CDC has continued its collaboration with the Centers for Medicare and Medicaid Services (CMS) to encourage and promote "standing orders" to improve influenza and pneumococcal vaccination levels in nursing homes and other healthcare facilities throughout the country. A standing order enables a facility to provide these vaccinations by appropriately qualified personnel without an individual prescription. In 2002, CDC and CMS completed a three year program to promote standing orders for Medicare patients in nursing homes. Initial data showed that standing orders are both more effective and more cost-effective than other methods for

increasing immunization coverage against influenza and invasive pneumococcal disease among nursing home residents. Based on the success of this work and recommendations from ACIP, CDC worked with CMS to change Medicare's regulatory structure to encourage the use of standing orders for flu and pneumococcal vaccines in nursing homes, home health agencies and hospitals.

2. CDC and the American Medical Association have co-sponsored the annual National Influenza Vaccine Summit for the past four years. The Summit includes over 90 partners and stakeholder organizations working together year-round to address the challenges associated with production, distribution and administration of influenza vaccine. Both the National Council on Aging and the American Association of Retired People has attended Summit meetings.
3. The Department of Health and Human Services (HHS) has made the elimination of racial and ethnic disparities in influenza and pneumoccocal vaccination coverage for people 65 years of age and older a priority. To address these disparities and to assist in reaching the 2010 national health goal of 90 percent influenza and pneumococcal vaccination rates among persons 65 years of age and older, CDC and other federal partners launched the Racial and Ethnic Adult Disparities Immunization Initiative (READII) in July 2002. The five READII demonstration sites have developed partnerships with public health professionals, medical providers and community organizations to develop and implement community-based interventions and innovative approaches to increasing immunization levels.

4. The SPARC initiative (Sickness Prevention Achieved through Regional Collaboration), established by the Berkshire Taconic Community Foundation in 1994, represents a collaboration of 75 organizations and businesses with an interest in disease prevention in a four-county region at the junction of Connecticut, Massachusetts, and New York (regional population: 636,000). SPARC has been working since 1995 to increase the use of influenza vaccination among persons aged greater than or equal to 65 years in each of the four counties through outreach and marketing campaigns. To promote pneumococcal vaccination, in 1997, SPARC's collaborators in two counties offered pneumococcal vaccination along with influenza vaccination, which more than doubled the prevalence of pneumococcal vaccination with only a modest increase in resources.
5. Beginning in 2001, CDC requested that states develop contingency plans in the event of an influenza vaccine shortage and provided written guidelines to assist them in planning. Should a shortage of influenza vaccine occur, CDC has plans for recommending tiered vaccination. The recommendations would be for providers to vaccinate high risk patients, which includes seniors, on a priority basis.
6. During the 2003-2004 influenza season, the American Lung Association (ALA) implemented a web-based directory of influenza vaccination clinics throughout the nation. There were a record-setting 150 million hits to the Flu Shot Directory during October and November, 2003. The ALA hopes to have even more participation during the 2004-2005 influenza season.
7. To prepare for this season the National Foundation for Infectious Diseases released a call to action to address low influenza vaccination coverage among health care professionals.

Communications for the 2004-2005 Influenza Season

CDC begins its annual national public-education campaign to promote the benefits of influenza vaccine and the most current influenza vaccination recommendations prior to the influenza season. Partnerships with health departments, medical societies, social service organizations and the private sector are important elements in the influenza communication efforts. Those aged 50 and older are a key target of the public education campaign. This season CDC is promoting four key messages to providers and the public:

- Influenza is a serious disease;
- Getting vaccinated every year is your best protection;
- Your vaccination helps protect others;
- October and November are the best months to get vaccinated.

Based on formative research, printed materials have been developed in both English and Spanish and made available on the CDC website. Many of these materials target seniors and use images and messages that resonate with this audience. A national media campaign, consisting of press conferences, teleconferences, news releases (video, audio and print), and radio advertisements, was launched this month for the upcoming season.

CDC takes steps to communicate issues regarding influenza to all possible audiences. We have a proactive campaign to keep health care providers and states informed as the season progresses through the dissemination of a series of CDC Health Updates and articles in CDC's weekly publication, Morbidity and Mortality Weekly Report (MMWR). These publications provide updates on U.S. influenza activity and address issues such as the importance of timely

vaccination, with priority placed on vaccinating persons at high risk for complications from influenza. They also provide guidelines for infection control and use of antiviral drugs.

Preparedness for 2004-2005 Influenza Season

Domestic influenza surveillance will be augmented this season with two new components: surveillance for pediatric hospitalizations and pediatric mortality reporting. In addition, we are expanding our capacity to identify new strains of influenza viruses more rapidly and evaluating vaccine effectiveness annually using prospective study methods so that reliable information is available on the match of the vaccine to current circulating strains.

While domestic and international health are inextricably linked, the fulfillment of CDC's domestic mission – to protect the health of the U.S. population – requires increased global awareness and collaborations with global partners. To that end, HHS and CDC recently undertook an initiative to build capacity for influenza surveillance in Asia. By expanding international surveillance networks and sharing of influenza virus isolates through the World Health Organization (WHO) surveillance network, we will increase our ability to detect new variants earlier, and thus generate more timely data with which to make vaccine decisions. At the same time, we will have the added benefit of early warnings of new viruses with pandemic potential or other infectious diseases. The investment has already proven fruitful as the surveillance network created for influenza played a key role in detecting and characterizing the spread of SARS.

Influenza Pandemic Planning

While preparing for the upcoming season, the possibility of an influenza pandemic must also be considered. The National Vaccine Program Office (NVPO) in the Department of Health and Human Services has responsibility for coordinating and ensuring collaboration among the many federal agencies involved in vaccine and immunization activities. Significant progress has been made in vaccinating America's seniors. More needs to be done. In August NVPO published the pandemic influenza preparedness and response plan for public comment in the Federal Register. This plan includes approaches for improving annual influenza disease control, including vaccine production, distribution, and administration.

Conclusion

Mr. Chairman, although the influenza season arrived earlier than usual last year, associated disease and death was on par with other recent years when influenza A(H3N2) viruses predominated. However, the impact on the health of Americans, especially seniors, remains far too high. Last season's media attention increased consumer awareness of the impact of this disease and demand for vaccine late in the influenza season. The challenges of last season and the recent report in JAMA concerning the morbidity and mortality caused by influenza during regular seasons highlights the urgency of improving the nation's capacity to respond to a catastrophic event such as an influenza pandemic.

To address the challenges we face, we need to be able to respond more rapidly than current vaccine production methods allow. In addition, we need to enhance our monitoring activities so we can detect virus variants earlier so they can be incorporated into annual vaccine formulations. We must continue to strengthen

our promotional efforts to educate the public about the importance of routine influenza immunization to create the demand to vaccinate high-risk individuals, alleviate surges in demand, and develop a consistent market so manufacturers can better gauge vaccine supply. We must convince our seniors and others at high risk for complications from influenza to get vaccinated annually. Our continuing collaboration with state and local public health partners, healthcare providers, and private sector partners will improve our nation's ability to plan and prepare for influenza.

Thank you again for holding this hearing on such an important public health issue. I encourage you, if you are in one of the groups recommended to be vaccinated, to get your own influenza vaccinations. Dr. Rodewald and I would be happy to respond to any questions you may have.

The CHAIRMAN. Well, Doctor, thank you very much for that testimony. Now let us turn to Pamela McInnes, deputy director, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases. That is a great title, Pamela. Welcome to the committee.

STATEMENT OF PAMELA M. MCINNES, DDS, MSC, DEPUTY DIRECTOR, DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, BETHESDA, MD

Dr. MCINNES. It is long. Thank you, so much. Mr. Chairman, thank you for the opportunity to discuss with you and the committee the role of the National Institutes of Health in combating influenza. The National Institute of Allergy and Infectious Diseases, fondly known as NIAID, a component of the NIH, is the lead Federal agency for conducting, supporting, and coordinating resource on influenza and other infectious diseases.

Influenza is a classic example of a reemerging disease. It is not a new disease but it continually changes. In most years, flu viruses that infect humans globally undergo small changes. If enough of these changes accumulate, the virus is able to escape the human immune response that resulted from prior exposure to influenza viruses or vaccination.

These changes are the basis of well-recognized patterns of influenza disease that occur every year. One of the population groups at risk of the serious complications of influenza is the group over 65 years of age.

Only three types of influenza viruses routinely circulate amongst humans. However, all known influenza A subtypes are common in the gastrointestinal tract of wild ducks. Because the replication machinery of the influenza virus is prone to errors as the virus multiplies, avian flu viruses can emerge that may be able to jump species into domestic poultry, farm animals and humans. H5N1 avian flu viruses made the jump directly from birds to humans in 1997 in Hong Kong, but because the virus did not acquire the ability to spread from human to human, only a limited number of deaths occurred.

Currently, H5N1 avian influenza virus in Vietnam and Thailand also have made the jump directly from bird to humans and has resulted in a 72 percent mortality rate. The fear is that the avian H5N1 and a commonly circulating human influenza virus might recombine resulting in the global spread of a new deadly influenza virus that can be spread among humans and to which the majority of the world will be susceptible, referred to as a pandemic strain.

The overall goal of the NAIAD influenza program is to support research that leads to more effective approaches for controlling influenza. This program has two major components, both of which are specified in the nation's draft Pandemic Influenza Preparedness and Response Plan.

The first component reflects long-standing programs for interpandemic influenza, including basic research, surveillance for the detection of animal and bird influenza viruses with pandemic potential, and the identification, development, and evaluation of rapid diagnostics new antiviral drugs and vaccines.

Because influenza is so easily transmitted, effective vaccines are essential to the control of annual flu epidemics. Although the current egg-based system used to produce licensed flu vaccines has been reliable, there is room for improvement. NIAID is supporting a number of research projects to develop flu vaccines that can be manufactured more rapidly and are more effective.

Recently, NIAID supported a clinical trial in older adults of a new influenza vaccine produced in a cell culture system as an alternative to manufacturing the vaccine in eggs. The positive results of this trial suggest that this new vaccine approach could be a viable alternative to the traditional egg-based influenza vaccine.

Although vaccination in the elderly population is very effective in preventing severe illness, complications and death, we know that elderly individuals are protected less effectively by vaccination that younger individuals. There is early research evidence that increased doses of vaccine in the elderly result in a higher level of protective antibodies against influenza virus.

NIAID is also supporting research to determine if a novel booster vaccination strategy would improve the efficacy of flu vaccines in the elderly.

The second component of NIAID's influenza program is geared to address the emergence of influenza viruses with pandemic potential in humans. NIAID has already begun to implement this carefully planned process in response to the H5N1 avian outbreak in southeast Asia.

An NIAID contract investigator used reverse genetics technology to generate a reference virus that has the characteristics of the H5N1 wild type virus but is safe for researchers and manufacturers to work with in the laboratory and in the manufacturing plant.

NIAID has provided this reference strain to the currently licensed and activated flu vaccine manufacturers, Aventis and Chiron. Under contract to NIAID, both of these manufacturers are developing pilot lots of the inactivated H5N1 vaccine. NIAID will test this vaccine in people for safety and the ability to raise antibodies. It is planned that one of the groups in the studies will be older adults. These actions are critical steps which will help prepare the Nation to respond to a pandemic influenza outbreak.

Mr. Chairman, thank you again for inviting me to discuss NIH's efforts to address the threat of influenza. In addition to the significant toll exacted by flu each year in the United States, the risk of pandemic influenza is significant and the consequences could be very serious.

Influenza is one among many ever-changing infectious disease threats confronting our nation and the world. Fortunately, much of what we learn from the study of one pathogen can often be applied to others. NIAID as the lead Federal agency for infectious diseases research constantly strives to improve its ability to respond to any infectious disease threat in concert with our colleagues at CDC and FDA.

I would be pleased to answer your questions. Thank you.

[The prepared statement of Dr. McInnes follows:]

Testimony
Before the Special Committee on Aging
United States Senate

NIH's Biomedical Research Response to Influenza

Statement of
Pamela McInnes, D.D.S., M.Sc. (Dent.)
Deputy Director
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases
National Institutes of Health
U.S. Department of Health and Human Services

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Tuesday, September 28, 2004

Introduction

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

Emerging and Re-emerging Infectious Diseases

Infectious diseases have afflicted humanity since ancient times, and they will continue to confront us as long as man and microbes co-exist. Unfortunately, the viruses, bacteria, and parasites that cause infectious diseases do not remain static, but continually and dramatically change over time as new pathogens emerge and as familiar ones (such as influenza) re-emerge with new properties or in unfamiliar settings. Such emerging and re-emerging infections have shaped the course of human history while causing incalculable misery and death.

Our ability to respond effectively to new infectious disease threats, whether they are emerging, re-emerging, or deliberately introduced, involves many different kinds of activities and many different organizations. From a public health perspective, surveillance and response are the key elements in controlling emerging and re-emerging infections and depend upon rapid detection and containment of pathogens in populations and the environment. Globally, such efforts are coordinated by the World Health Organization (WHO). In the United States, such efforts are led by the Centers for Disease Control and Prevention (CDC), which along with state and local health departments and other agencies recently have made significant strides in national disease surveillance and response capacity. Physicians, nurses, other health care workers and hospitals also must be integrated to respond in a coordinated manner to an outbreak, and the pharmaceutical industry must be fully engaged to develop and manufacture needed diagnostic tools, therapeutics, and vaccines. Within the Department of Health and Human Services (HHS), NIH, CDC, the Food and Drug Administration (FDA), and other agencies all have distinct but complementary roles to play, and have a long history of cooperation. The NIH concentrates on a strong and focused research program that is critical to preventing and controlling these infectious disease threats.

The conduct, support, and coordination of basic, translational, and applied infectious disease research is the primary responsibility of NIAID. First and foremost, NIAID supports basic and clinical research, which is needed to understand how pathogens

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

Influenza Research Activities at NIAID

Influenza is a classic example of a re-emerging disease; it is not a new disease, but it continually changes. In most years, influenza viruses that typically infect humans globally undergo small changes in the properties of their surface proteins. If enough of these changes accumulate, the virus is able to escape the human immune response that resulted from prior exposure to influenza viruses or vaccination. This is referred to as "antigenic drift" and it is the basis of well-recognized patterns of influenza disease that occur every year and cause significant mortality and morbidity. According to new estimates, influenza infections are estimated to result in an average of 36,000 deaths and over 200,000 hospitalizations each year in the United States, and the WHO estimates that the annual average number of deaths worldwide is approximately 500,000. One of the population groups at risk of the serious complications of influenza

is the group over 65 years of age. The CDC recommends that this age group be vaccinated against influenza each year, and the HHS has set a goal of 90% vaccination coverage for them. However, we know that currently only two-thirds of this group is vaccinated each year.

Although only three types of influenza viruses routinely circulate among humans, all known influenza A subtypes are endemic in the gastrointestinal tract of wild ducks. Because the replication machinery of the influenza virus is error prone, as the virus multiplies, avian influenza viruses can emerge that may be able to jump species into domestic poultry, farm animals such as pigs, and humans. When an influenza virus jumps species from an animal such as a chicken to a human, it usually is a "dead end" infection in that the virus cannot readily transmit further from human to human. Avian influenza viruses made the jump directly from birds to humans in 1997, but because the virus did not acquire the ability to spread from human to human, only a limited number of deaths (6 out of 18 confirmed cases) occurred. Currently, H5N1 avian influenza viruses in Vietnam and Thailand also have made the jump directly from birds to humans and have resulted in deaths of 28 out of 39 confirmed cases (as of September 7) representing a 72% mortality rate. The fear is that the avian H5N1 and a commonly circulating human influenza virus such as H3N2 might recombine if they were to simultaneously co-infect a person, resulting in the global spread of a new, deadly influenza virus that can be spread among humans and to which the majority of the world will be susceptible, referred to as a pandemic strain. This type of significant change in

the antigenic makeup of the virus, which can result in a pandemic, is referred to as an "antigenic shift".

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

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

- **Basic Research.** NIAID supports many basic research projects aimed at understanding how the influenza virus replicates, interacts with the host, stimulates an immune response and evolves into new strains. Results from these studies provide the information needed for the design of new antiviral drugs, diagnostics, and vaccines.

- **Antiviral Drugs.** NIAID currently supports the identification, development and evaluation of new antivirals against influenza including the screening of new drug candidates to see if they are active against the virus both in laboratory cells and in animals. We also are developing novel broad-spectrum therapeutics intended to work against many influenza virus strains; some of these target viral entry into human cells, while others specifically attack and degrade the viral genome. Development and evaluation of a combination antiviral regimen against potential pandemic influenza strains is also now under way.

- **Diagnostics.** NIAID supports the development of rapid, ultra-sensitive devices to detect influenza virus infection. Although we are at an early stage of development, these devices will allow detection of newly emerging viral mutants and discrimination between different antigenic sub-types. Other diagnostics in development will have the ability to discriminate between influenza and other pathogens that cause so-called

"flu-like symptoms", such as SARS. A more rapid identification of the disease-causing agent will allow for faster and more effective treatment and control measures.

- **Vaccines.** Because influenza is so easily transmitted, effective vaccines are essential to the control of annual influenza epidemics. The current egg-based system used to produce licensed influenza vaccines—despite being reliable for more than 50 years—can be improved. Limitations of the current system include: (1) a lengthy manufacturing process; (2) the need to select which virus strains will be in the vaccine at least six months in advance of the influenza season; (3) the need to produce enough new influenza vaccine each year to meet the continually increasing demand (about 100 million doses in 2004); and (4) the requirement of hundreds of millions of fertilized chicken eggs to manufacture the vaccine. This early decision about which strains to include in the influenza vaccine will not always be correct, and the long lead time required to produce the vaccine makes mid-stream corrective action impossible. Additional limitations could include allergenicity of eggs in some individuals and inability to use eggs for propagation of viruses lethal to chickens.

NIAID is currently supporting a number of research projects aimed at developing influenza vaccines that can be manufactured more rapidly, are more broadly cross-protective, and are more effective. The use of reverse genetics—a tool developed by NIAID-supported scientists—holds the promise for more rapid generation of high-yielding vaccine candidates that match the anticipated epidemic strain. Reverse genetics also can be used to turn highly pathogenic influenza viruses into vaccine candidates more suitable for vaccine manufacturing by removing or modifying certain virulence gene sequences; laboratories around the world have used this technique to prepare vaccine candidates against the H5N1 viruses that emerged in Asia in 2004.

NIAID also supports the development of new influenza vaccine technologies. Recently, NIAID supported a Phase II clinical trial in older adults of a new influenza vaccine produced in a cell culture system, as an alternative to manufacturing the vaccine in eggs. The results of this trial suggest that this new vaccine approach could be a viable alternative to the traditional egg-based influenza vaccine. Other studies have focused on the development of broadly protective vaccines that induce protection against multiple strains of influenza and, therefore, do not need to be updated yearly.

NIAID is supporting studies to improve the effectiveness of current inactivated vaccines in elderly individuals, the population that frequently accounts for up to 90% of the influenza deaths each year in the United States. Although vaccination in this population is very effective in preventing severe illness, secondary complications, and death, we have seen that elderly individuals are protected less effectively by vaccination than younger individuals. NIAID has recently supported a clinical trial in the elderly to evaluate doses of the inactivated vaccine with increased antigen content. The results of this trial suggest that increased doses of vaccine in this population result in a higher level of protective antibodies against influenza virus. Another study is currently being supported to evaluate the effect of exercise on the immune response to influenza vaccination in older adults. The results suggest that older adults who participate in regular exercise programs had a higher antibody response to the vaccine than did their sedentary counterparts. NIAID has recently supported a research grant to elucidate why the elderly respond less effectively to vaccination and to determine if a novel booster vaccination strategy would improve efficacy in the elderly.

Because NIAID has had remarkable success in the past with groundbreaking vaccine research—including advances that led to hepatitis B, *Haemophilus influenzae b*, pneumoccocal pneumonia, and acellular

pertussis vaccines, as well as the new live attenuated intranasal influenza vaccine approved by the FDA last year—I am confident that one of the approaches we are pursuing also will lead to a useful, "next-generation" influenza vaccine that can easily be adapted to emerging influenza strains.

- **Surveillance and Epidemiology.** The threat from influenza, like virtually all emerging and re-emerging infectious disease threats, is global in scope. For this reason, NIAID has expanded its activities in other countries in recent years. Through a contract for pandemic influenza preparedness, NIAID supports a long-standing program in Hong Kong to detect the emergence of influenza viruses with pandemic potential in animals. Under this program, Dr. Robert Webster of St. Jude Children's Research Hospital in Memphis, Tennessee, leads a group that detected the re-emergence of highly pathogenic H5N1 avian strains in this area in 2002 and 2003, and was instrumental in the early detection and characterization of the SARS coronavirus in 2003. This underscores the concept that research on one type of infectious disease often supports or can be applied to research on the other types of infectious diseases, whether newly emerging, re-emerging, or deliberately introduced.

The second component of NIAID's Influenza Program is geared to address the emergence of influenza viruses with pandemic potential in humans. The U.S. Pandemic

Influenza Preparedness and Response Plan describes specific roles for NIAID, should a pandemic influenza strain emerge and a Pandemic Alert be declared. Foremost among these responsibilities is to help develop and produce an effective vaccine as rapidly as possible. Under this plan, NIAID would assist in the characterization of the newly emerging influenza strain, create vaccine candidates, develop investigational lots of candidates, and produce and distribute research reagents for use by vaccine researchers in academic and pharmaceutical industry laboratories. NIAID would also work with industry to produce and conduct clinical studies on vaccine candidates. NIAID-supported scientists will also evaluate the susceptibility of the newly emerging virus to the currently available influenza drugs and new drug candidates. NIAID has already begun to implement this carefully-planned process in response to the avian influenza outbreak in Southeast Asia.

NIAID utilized reverse genetics to generate a reference strain that has the antigenic characteristics on the H5N1 avian influenza strain, but is safe for researchers to work with in the lab. NIAID has provided the reference strain to currently licensed influenza vaccine manufacturers, Aventis Pasteur, Inc. and Chiron Corporation. Under contract, both manufacturers are developing pilot lots of inactivated H5N1 vaccine. NIAID will test this vaccine for safety and immunogenicity in humans; it is planned that one of the groups in the study will be older adults. HHS recently awarded a contract to Aventis to manufacture and store 2 million doses of this vaccine. These actions are critical steps which will help prepare the nation to respond to a pandemic influenza outbreak. All of

this work is done in close coordination with CDC, FDA, and WHO. This coordination is needed if a safe and effective vaccine is to be available to the public as soon as possible.

Conclusion

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

I would be pleased to answer your questions.

The CHAIRMAN. Pamela, thank you very much. But before I do question either of you, let me turn to my colleague Evan Bayh who has joined us. I had mentioned in my opening statement that Evan was instrumental in introducing S. 2038, the Flu Protection Act of 1904. I joined with him as co-sponsor.

Evan, any opening comments you would wish to make, and then if you want to start, you can lead off with questions.

STATEMENT OF SENATOR EVAN BAYH

Senator BAYH. Well, thank you very much, Mr. Chairman. Only to say I appreciate your leadership on this issue and I appreciate the time of the panelists, both on this panel and panel two.

We are really here today because of some of the problems uncovered as a result of the flu season last year. We want to encourage those who are in at-risk populations to receive immunization and to really ensure that the shortage that occurred and the ensuing sort of mini-panic on the part of the public does not happen again.

So Mr. Chairman, I appreciated our opportunity to work together and this hearing really before the advent of flu season to try and encourage. Basically we have one message to people at home today. It is go out and get immunized. Vitally important.

I would like to begin, I just have a couple of questions, Mr. Chairman. You know the old adage, "fool me once, shame on you; fool me twice, shame on me." Can any of you assure us that we have enough doses of vaccine to get us through this flu season after the shortage we experienced last year?

Dr. OSTROFF. Well, the answer to that question is that we ultimately will not know until we are actually through the flu season. As I mentioned in my statement, we feel that we are in much better shape than we were last year, given that the amount of vaccine that is being produced far exceeds what was produced last year, and we know that that vaccine is now being distributed.

Senator BAYH. Mr. Ostroff, forgive me. If everyone who we are recommending were to receive the vaccine, how many vaccine doses would that be in our country?

Dr. OSTROFF. Well, that would be 185 million.

Senator BAYH. How many doses are we estimating it will produce this year?

Dr. OSTROFF. Currently 100 million.

Senator BAYH. So we know that we are 85 million short of the number of doses needed to cover all the people we are encouraging to get vaccinated?

Dr. OSTROFF. You are absolutely correct, Senator.

Senator BAYH. That seems to me to be a little cognitive dissonance here.

Dr. OSTROFF. The difficulty is that there is always a conflict between supply and demand, and certainly with the current production of the vaccine, the amount that is produced is the amount that is anticipated to be demanded by the public.

We had several seasons in a row before last season where the supply far exceeded the demand and unfortunately a lot of that vaccine did not go into people's arms.

The CHAIRMAN. Yes. Could we put up that chart because Evan asked a very important question, and you brought a chart along that I thought was interesting.

Dr. OSTROFF. Right.

The CHAIRMAN. That reflected the difference here.

Dr. OSTROFF. As you can see, for several years, there was an excess that was building up.

Senator BAYH. Sure. That is the tension, as I understand it.

Dr. OSTROFF. Correct.

Senator BAYH. The companies, of course, need to keep an eye on the bottom line and if they have had an experience of producing too many doses, then obviously they have learned from that, but then you get a year like last where we are caught short and so the trick is to either have better forecasting tools or to try to assure the producers that they are not going to get left holding the bag if we have a year like last year.

That is why I thought the mechanism included in our bill, Mr. Chairman, was the right way to approach this, to basically lend some certainty to the producers. I gather that instead we have gone down a different path of the government purchasing a fixed number of doses—is that correct—to try and make up any shortfalls should one occur?

Dr. OSTROFF. That is correct.

Senator BAYH. How many doses did the government purchase?

Dr. RODEWALD. We have a contract for eight million doses of vaccine through the routine program, and then as an insurance policy in response to what happened last year, we have a contract for 4.5 million additional doses of influenza vaccine, half of which will be available December 1 and half of which will be available before January 1.

We think that will go a long way to help if there is unanticipated emergency late season demand like we had last year. I think this point about demand and supply is a very important one because I believe the best way to increase the production of vaccine is to increase the demand of vaccine, but it has to be done in a way that is orchestrated such that we do not outstrip the production by expanding our recommendations and thereby, pushing too much demand at one time.

For example, the new childhood recommendation will help raise the demand for vaccine and ultimately we would like to weave influenza vaccination much more closely into the fabric of society. Increased demand will increase production and will not leave the manufacturers with a lot of unused vaccine at the end of each season.

Senator BAYH. What was the reasoning behind choosing to purchase a fixed number as opposed to purchasing the unused numbers of doses?

Dr. RODEWALD. I do not know the answer to the question whether it was presented as an option, but we thought that a fixed number of——

Senator BAYH. It was the option in our bill.

Dr. RODEWALD. The fixed number was selected because we were able to fund this through the Vaccines for Children program, which

is an entitlement program to children, and this allowed us to buy vaccine that we could guarantee to be distributed in December.

Senator BAYH. I am curious, Mr.—again, we all want the same things here. We all want to ensure that there is enough supply to cover people in years that are a little, hopefully, aberrant like last year, and at the same time minimize the cost to the taxpayers.

I am just curious as to why the method of selecting or trying to divine a fixed number to purchase was chosen over instead of ensuring the producers that we would purchase any unused quantities?

Just curious as to why one was chosen over the other? We all want to choose the right course, whatever that might be.

Dr. OSTROFF. Well, again, our ultimate goal is to make sure that we do not have some of the same problems that we did last year. We all want to make sure that there is an adequate supply of vaccine, and in response to your earlier comment, when we have a goal of 90 percent coverage, we all want to be able to work together to move toward that 90 percent or even 100 percent coverage, and there is no question that that is going to take a concerted effort on everybody's part to encourage people to get vaccinated as well as to assure that there is vaccine available to be able to deliver to them.

Senator BAYH. Mr. Chairman, you have been very gracious, and I see the red light is on, so I would like to thank the panelists again for your work in this area and your presence here today.

The CHAIRMAN. Evan, thank you very much. Let me turn to another one our colleagues who has joined us, Senator Tom Carper. Tom, do you have any opening comments and questions of this first panel?

Senator CARPER. I have a couple of questions, if I could.

The CHAIRMAN. Please proceed.

Senator CARPER. To our panelists, thanks very, very much for joining us this morning and for your good work in this effort. I am not sure who to direct this question to. Maybe I should direct it to you, Ms. McInnes, and if I am wrong, then maybe one of your colleagues will take it on.

Could you just start off by talking to me about the nature of the disease itself, the diseases, the viruses that we are trying to contain here?

Dr. MCINNES. Sure. Influenza is one of the important respiratory viruses. It is spread by a respiratory route. It is a disease that affects the mucosal, the lining of the respiratory tract, and it replicates when in human and it also has an unfortunate——

Senator CARPER. When you say it replicates, just explain to us.

Dr. MCINNES. To multiply, copies itself and multiplies.

Senator CARPER. Once it is inside of a body?

Dr. MCINNES. Yes.

Senator CARPER. OK.

Dr. MCINNES. It has an unfortunate part of its disease progression where it actually, in the cells that line your nose and your epithelium and your tissues in your lungs, there are little hair-like fibers that are called cilia, and they are very important in protecting your body against infection, and one of the byproducts of influenza is that it actually paralyzes those cilia so you end up with a res-

piratory system that is now vulnerable to so many things in addition to influenza, and many of the deaths associated with influenza are started with flu and then you will have a secondary bacterial infection that may come in on top of that influenza infection.

Classically, people have fevers, they have muscle aches, chills, sort of almost bone-cramping kinds of muscle pains can happen. The fever goes on for several days and then normally healthy people who have normal immune systems will mount an immune response to that and recover.

People who do not have a normal and high functioning immune system very often go on and develop secondary infections and have a much harder time dealing with influenza as a disease.

Senator CARPER. How does a vaccine work to combat the infection?

Dr. MCINNES. Most of the vaccine that is used in this country is the inactivated vaccine, and that is a killed vaccine.

Senator CARPER. A what?

Dr. MCINNES. It is a killed vaccine.

Senator CARPER. What does that mean?

Dr. MCINNES. So we grow up the influenza virus in eggs, and then it is taken out of the eggs, and it is inactivated with a procedure whereby the virus is actually killed.

So you have an inert virus and pieces of the virus in the vaccine, and what that does is that it stimulates the antibody response without itself causing an infection. So what you do is you hope that you have—we know very well that antibodies are a very, very important protective mechanism against the live virus, and so by vaccinating you induce an immune response with good antibodies so that if you encounter the virus, you then have a heightened way to respond to the virus and hopefully not become ill.

Senator CARPER. The vaccine that was developed, for example, to fight the flu last year——

Dr. MCINNES. Yes.

Senator CARPER [continuing]. Is it likely to work this year and next year and the year after that? Do we have to continue to, I guess, are we looking for continuous improvement in our vaccine?

Dr. MCINNES. Flu is one of those things where every year we monitor for what we think may be the next viruses and, no, there are subtle changes that happen in these influenza viruses every year, and so very early in the year, we are looking at the data that have come out from other parts of the world and we may make recommendations to change the virus a little bit. There are three virus components in each annual year's flu vaccine. Sometimes they stay the same. Sometimes they are changed. Sometimes just one strain is changed. This year actually two of the strains will be changed from last year's vaccine.

Senator CARPER. All right. To your colleagues and to you, Ms. McInnes, what would be your take-away for us as we walk out of this hearing knowing that we are going out and face the challenges the world poses for us and our country? What would you want to be our take-away from this hearing? If we remember nothing else, what would you want us to remember?

Dr. OSTROFF. My message as we sit here on September 28, is that we need to roll up our sleeves. We need to roll up our sleeves

and all work together to build the vaccine supply and we need to roll up our sleeves and get vaccinated. Now is the time to get started.

Senator CARPER. All right.

Dr. RODEWALD. Influenza vaccination is the safest and most effective way to protect not only yourself from influenza disease but also your loved ones from influenza disease.

Senator CARPER. All right. Thanks. Ms. McInnes?

Dr. MCINNES. I think those are wonderful.

Senator CARPER. Were you born in Delaware? Is that a Delaware accent I hear or is that Idaho or is that Indiana?

Dr. MCINNES. Actually, no, I was born in a very small town in South Africa.

Senator CARPER. No kidding. I thought you might be. How did you end up here?

Dr. MCINNES. I married an American.

Senator CARPER. So did I. [Laughter.]

That is good. We are glad you are here. We are glad you are all here. Thank you very much for your testimony and for your help. Thank you.

The CHAIRMAN. Well, let me ask some questions because I think the thing that is most profound, and I think both of my colleagues and I realize this, that this is a killer of elderly Americans. It ought to be viewed like that, and I would wish that older Americans would view it, that as they age, they develop a higher risk and the statistics are just black and white when it comes to that issue.

Doctor, you stated that the majority of influenza strains that CDC has characterized this year are well matched to the vaccine that has been produced for the coming season. What is the possibility that an unmatched strain could still appear?

Dr. OSTROFF. Well, Senator, in response to that question, the one thing that we always know about flu is that it can be very unpredictable. So predicting what might happen during the coming flu season is always an imperfect science: when the flu season will really get started, where it will occur first in the country, and which strain is going to be causing the majority of disease.

The CHAIRMAN. When that begins to appear, what do you do?

Dr. OSTROFF. Well, we work year-round monitoring for cases of influenza. We used to just do it starting on October 1 and then we would continue to monitor through May 1, but we've now been moving towards year-round monitoring because we recognize that even up here in the temperate part of North America there is the occasional case of flu that occurs during an unusual time of the year, so we need to know about that.

We need to know what the strain is that is causing the disease and be prepared to respond to that. So we are constantly in this country monitoring for influenza, and we are looking for just the circumstances that you mentioned is the problem that we have is that we need to let the manufacturers know so far in advance which strains we predict are going to be circulating six to eight to nine months later, so that they can go through the entire manufacturing process and end up with enough vaccine in the fall to be able to vaccinate.

The CHAIRMAN. From the time you discover or let us say you or a discovery occurs that you have got a different form and you notify the manufacturer, how long does it take for a vaccine to be able to get to the street?

Dr. OSTROFF. Well, the short answer to that is it depends, and so there is no single answer. It depends when during the season that strain is recognized in relation to where the manufacturers happen to be in the manufacturing process.

In general, it will take a good four to six months to make those types of changes given the current system for vaccine production in this country. However, I will point out that our predictive capacity is much, much better than it used to be because the monitoring systems, not only here in North America, but also especially in Asia, are much, much better than they used to be, and so the predictions in virtually all years, and I say virtually because nothing is 100 percent, between what strains should go into the vaccine and what actually circulates have been extremely good essentially every year. Last year, unfortunately, was one of the anomalies.

The CHAIRMAN. What is—I guess let me put it this way—how do we deal with only 38 percent of our health care providers receiving flu vaccinations? I mean the connectivity between a healthcare provider and his or her client, the senior citizen?

How do we address that?

Dr. OSTROFF. Well, I must confess all of us have been perplexed about why we have such difficulty getting that number higher. I certainly get my flu vaccine every year and have done so for years. I am a healthcare provider and it is the appropriate thing to do, not only to protect myself so that I do not have lost work time, but in particular, to protect those around me that I care for, who are at higher risk of developing the complications.

I myself find it in inexcusable that a healthcare worker would not heed that message and do something to protect their patients in that way. We know, I think from experience, that the more opportunities that there are, and the easier that we make it for healthcare workers to get the vaccine, the more likely they are to actually accept it. So having organized vaccination campaigns in healthcare facilities, particularly acute healthcare facilities, nursing homes, et cetera, is the way to boost coverage.

The CHAIRMAN. How many states have developed contingency plans in light of the whole influenza issue; do you know?

Dr. OSTROFF. It depends what you mean by contingency plans and I will ask Dr. Rodewald to amplify my answer. We have been encouraging all states to develop plans to deal with shortages, yes.

The CHAIRMAN. By that, I mean obviously if we get into a shortage environment and you have a limiting factor out there being the availability of vaccines——

Dr. OSTROFF. Right.

The CHAIRMAN [continuing]. How do we deal with that more frail or fragile or susceptible population, and what is being done in that regard if we get caught once again?

Dr. OSTROFF. Right. Go ahead.

Dr. RODEWALD. We have asked all the states to develop contingency plans in order to handle vaccination and vaccine shortages

and the states respond in their grant applications to CDC for how they are going to do this.

The CHAIRMAN. How many have done this to date?

Dr. RODEWALD. I do not know the exact number, but I think pretty much all of the states have plans for how they will handle a shortage, but I think the other part of the equation is to recognize that about 95 percent of this vaccine goes out through the private sector, and so close collaboration between the private sector distributors for the vaccine and the vaccine manufacturers in the Public Health Department and providers is essential, so we are working with the top 20 distributors to monitor how the vaccine is going out and in the case of a shortage what we will end up encouraging to have happen is that the distributors will send some vaccine to all the providers so that all the vaccinators can be working as best they can rather than giving a few providers a lot of vaccine, and some providers no vaccines.

So I think working collaboratively with the private sector has been a key to this, and the lessons for how to meter out this vaccine were learned in the childhood program where we have had to deal with shortages over the past two to three years, and metering out vaccine has been one of the more successful strategies there.

The CHAIRMAN. All of us are concerned about shortages or availability to a vulnerable population. So let me ask this of all of you because this is a question where we probe a bit. Media reports of influenza caused deaths seemed last year to be a significant factor in the shortage because with that alarm sent off, people rushed out. How can the media cover the seriousness of this issue without causing undue panic because clearly it is my opinion that the seriousness of it has to be understood or we should try to have it understood?

Dr. OSTROFF. My answer to that would be to report responsibly both information on flu as well as what people can do to reduce their risk. You want to avoid having a large cohort of individuals that did not heed the message to get flu vaccine at a time when the flu vaccine was widely available, and then at the last minute have a large deluge of individuals who then have to shop around looking for a place that has remaining vaccine.

The CHAIRMAN. Sure.

Dr. OSTROFF. This is the time to start getting your flu vaccine. The other important message is that not everybody has to get the vaccine at the same time. So we strongly encourage that people should be vaccinated well into the influenza season and one should never think that it is too late to get vaccinated.

The CHAIRMAN. Pamela, any additional comment to that?

Dr. MCINNES. No, I think if any message could go out about heeding what happened last year and not waiting until too late would be very, very welcome.

Dr. OSTROFF. Then one other message that I would get out there.

The CHAIRMAN. Yes.

Dr. OSTROFF. There is still a widespread belief that you can get the flu from getting the vaccine. As was pointed out, this is not the case. So we should not have anyone out there that has any concerns about developing the flu after getting the vaccine.

The CHAIRMAN. Well, that is a great lead-in to my next question, and the question is of you, Dr. McInnes, the available literature in this area raises the question of vaccine effectiveness for older people. It concerns me that the population in greatest need responds more poorly to the available vaccines, and I have heard it said in elderly populations that I know, "Well, I don't know that I want that, it might cause me to get it," type of thing. Can you tell us more about new vaccines being produced that are especially for the elderly?

Dr. MCINNES. Yes, I think we know very clearly that the more antibody you can stimulate with the vaccine, the better will be your chances of not becoming ill from influenza. You may become infected, but the disease may not be as severe, and we know the biggest impact from flu vaccine in the elderly is to prevent serious disease, hospitalizations, and death.

We still get people who are vaccinated who become infected with influenza, but one hopes that they have a more mild form of the disease. Clearly, the efficacy of the vaccine in terms of preventing any disease in the elderly is lower than in younger adults. We have very nice data to show that if you increase the amount of the components of the flu vaccine, you can stimulate more antibody in the elderly, and this is now a strong focus of ours in collaboration with the manufacturers to look at alternative formulations of vaccine that perhaps need to be twofold, threefold, fourfold in concentration compared to what is currently delivered now. So that is something that I think is quite practical and will probably have a good payoff.

The effect of adjuvants, which enhance the response, have been somewhat disappointing with regard to influenza vaccine in general, not just in the elderly. There is also the question on whether one might need to give a booster dose of vaccine to the elderly, and so instead of a one-dose regimen, could you do a two-dose regimen.

So both of those strategies are being explored currently.

The CHAIRMAN. I appreciate that, but we are still dealing with the complication of getting the first vaccination.

Dr. MCINNES. Absolutely.

The CHAIRMAN. Let alone a second vaccination.

Dr. MCINNES. Absolutely.

The CHAIRMAN. Yes. If you have to choose the most promising area of research, what are you most excited about? What shows the greater promise at this point?

Dr. MCINNES. In terms of influenza, we are very excited about, in fact, three areas, one of which is this tantalizing data about the ability to mount an improved immune response in the elderly by concentrating the vaccine, and that is something we will explore very aggressively.

The live attenuated influenza vaccines which are on the market now and last year were out for the first time, unfortunately do not look that promising for the elderly. The response does not look that promising, but shows great promise in the pediatric population which might help alleviate some of the vaccine availability issue. More of the inactivated vaccine could be available for the other populations.

Then third, in terms of new technologies, both in how we manufacture vaccines that might increase the amount of vaccine that is

available, the speed of our ability to make vaccines by being able to engineer the starting viruses will be probably critical, not only in producing inter-pandemic vaccines, but certainly in being able to respond to a pandemic situation.

The CHAIRMAN. Well, we thank you all very much, and Dr. Ostroff, we are going to let you have the last word, and ask you to repeat. The most important part of your message to the public today was?

Dr. OSTROFF. Roll up your sleeves and get vaccinated.

The CHAIRMAN. Repeat that, please, and louder.

Dr. OSTROFF. Roll up your sleeves and get vaccinated, and I will add that hopefully we can encourage all Members of Congress that fit into one of those high-risk groups to help us do that.

The CHAIRMAN. I thank you all very much for being here.

Dr. OSTROFF. Thank you, Senator.

Dr. MCINNES. Thank you.

The CHAIRMAN. I will ask our second panel to please come forward. Well, again, welcome to our committee. As I said earlier, our second panel, is comprised of Janet Heinrich, Director of Healthcare and Public Health Issues at the Government Accounting Office. I am also pleased to welcome Carol Moehrle, one of my constituents from Idaho, District Director for the North Central District Health Department, located out of Lewiston, ID, in the north end of our state. Last, and I think very importantly for this committee and for our public to hear, from Dr. Howard Pien, CEO and President of Chiron?

Dr. PIEN. Perfect.

The CHAIRMAN. Chiron Corporation. So again, to all of you welcome. Janet, would you please proceed?

STATEMENT OF JANET HEINRICH, DIRECTOR, HEALTHCARE AND PUBLIC HEALTH ISSUES, GOVERNMENT ACCOUNTABILITY OFFICE, WASHINGTON, DC

Ms. HEINRICH. Mr. Chairman, it is a pleasure to be here today as you discuss issues regarding the annual production and distribution of flu vaccine and preparedness for an influenza pandemic. Each year, influenza viruses are associated with deaths and hospitalizations, as we have heard, especially for persons age 65 and over.

The best way to prevent influenza is to be vaccinated each year. In the past, this country experienced periods when the demand for flu vaccine exceeded supply. There has also been increased concern about the prospect of an influenza pandemic which many experts believe to be inevitable.

Experts have raised concerns about the ability of our public health system to detect and respond to emerging infectious diseases such as pandemic flu. You have asked us to comment on these issues based on our previous work.

I will discuss issues related to supply, demand, distribution of flu vaccine, and review the pandemic plan recently released. For the current flu season, CDC is recommending that about 185 million people receive vaccine. It is generally widely available in the fall, and in the past about two-thirds of flu shots were administered in healthcare settings such as doctors' offices and clinics.

About a third were given in other locations such as stores or community settings. Most vaccine distribution and administration are accomplished within the private sector, with relatively small amounts being purchased by CDC or by state and local health departments.

Ensuring an adequate and timely supply of vaccine is a difficult task that has become more challenging with only a few manufacturers. Problems at one or more companies can upset the fall delivery of and flu vaccine cause unnecessary fluctuations in who has ready access to the vaccine.

Matching supply and demand is also a challenge. For example, in 2000–2001, when a substantial portion of flu vaccine was distributed much later than usual because of manufacturing problems, temporary shortages were followed by decreased demand as more vaccine became available later.

Last year's shortages, as we have heard, were attributed to an unexpected severe flu season and concerns about the deaths of children.

Our work has also found that there is no mechanism in place to ensure distribution of flu vaccine to high risk individuals before others when there is a short supply. For example, when the supply was not sufficient in the fall of 2000, focusing distribution on high risk individuals was difficult because all types of providers served at least some high risk individuals. Some physicians and public health officials were upset when the local grocery store was offering flu shots to anyone when they, the healthcare providers, were unable to obtain vaccine for their high-risk patients.

While CDC has taken some steps to recommend targeting vaccine when there are shortages, the situation is no different today.

In regards to pandemic planning, the new plan describes Federal roles and responsibilities in responding to a pandemic and provides guidance to state and local health departments. Although the draft plan is comprehensive in scope, it leaves some important decisions about the purchase, distribution, and administration of vaccines unresolved.

Consequently, states are left to make their own decisions, potentially compromising the timing and adequacy of a response to a pandemic. For example, the draft plan does not establish a definitive Federal role in the purchase and distribution of vaccine. Instead, different options are discussed.

The plan delegates to the states responsibility for distribution of vaccine. Among the current state plans, and there are only a few of those, we found no consistency in terms of their procurement and distribution of vaccine and the relative role of the Federal Government.

In addition, the plan does not identify priority groups to receive initial doses of vaccine. According to HHS officials, prioritization would be an iterative process and will be tied to vaccine availability in the progression of the pandemic. While recognizing that there is a need for flexibility, state officials have consistently told us that a lack of detailed guidance makes it difficult for states to plan.

In conclusion, ensuring an adequate and timely supply of vaccine to protect seniors and others from flu-related complications con-

tinues to be a challenge. Despite efforts by CDC and others, there remains no system to ensure that persons at high risk for complications receive flu vaccine first.

These vaccine supply and distribution problems may become especially acute in a pandemic. The absence of more detail in such issues as purchase and distribution creates uncertainty for the states with implications for adequate preparedness for a pandemic.

That is my statement. I am happy to answer any questions.

[The prepared statement of Ms. Heinrich follows:]

United States Government Accountability Office

GAO

Testimony

Before the Special Committee on Aging, U.S. Senate

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INFECTIOUS DISEASE PREPAREDNESS

Federal Challenges in Responding to Influenza Outbreaks

Statement of Janet Heinrich
Director, Health Care—Public Health Issues

GAO-04-1100T

Mr. Chairman and Members of the Committee:

I am pleased to be here today as you discuss issues regarding the annual production and distribution of flu vaccine and preparedness for a worldwide influenza epidemic—known as a pandemic. Each year, influenza viruses cause outbreaks in the United States and elsewhere in the world. Influenza is associated with an average of 36,000 deaths and more than 200,000 hospitalizations each year in the United States. Persons aged 65 and older are involved in more than 9 of every 10 deaths and 1 of every 2 hospitalizations related to influenza. The best way to prevent influenza is to be vaccinated each fall. In the 2000-01 flu season, and again in last year's flu season, this country experienced periods when the demand for flu vaccine exceeded the supply, and there is concern about the availability of vaccines for this and future flu seasons.

There has also been increased concern about the prospect of an influenza pandemic, which many experts believe to be inevitable. Pandemic influenza, which arises periodically, but unpredictably, from a major genetic change in the virus, results in a strain that can cause worldwide disease and death. Three influenza pandemics occurred in the twentieth century. The worst occurred in 1918 (Spanish flu) and killed more than 20 million people worldwide and about 675,000 people in the United States. The pandemics of 1957 (Asian flu) and 1968 (Hong Kong flu) caused fewer fatalities—70,000 and 34,000, respectively, in the United States. Some experts believe that the next pandemic could be spawned by the recurring avian flu in Asia.[1] They estimate that the pandemic could kill up to 207,000 people in the United States and cause major social disruption. Public health experts have raised concerns about the ability of the nation's public health system to detect and respond to emerging infectious disease threats such as pandemic influenza.[2]

You have asked us to provide our perspective on flu vaccine availability and preparedness for this year's flu season and an influenza pandemic. In this testimony, I will (1) discuss issues related to supply, demand, and

[1]Department of Health and Human Services, "HHS Orders Avian Flu Vaccine as Preventive Measure," http://www.os.dhhs.gov/news/press/2004pres/20040921a.html (downloaded Sept. 26, 2004).

[2]See GAO, *SARS Outbreak: Improvements to Public Health Capacity Are Needed for Responding to Bioterrorism and Emerging Infectious Diseases*, GAO-03-769T (Washington, D.C.: May 7, 2003).

distribution of vaccine for a regular flu season and (2) assess the federal plan to respond to an influenza pandemic.

My remarks are based on reports and testimony we have issued since October 2000,[3] as well as work conducted to update key information. Our prior work on flu vaccine included interviews with and analysis of information provided by Department of Health and Human Services (HHS) officials, vaccine manufacturers, medical distributors and their trade associations, companies that provide flu shots at retail outlets and work sites, physician and other professional associations, and other purchasers. We also surveyed physician group practices and interviewed health department officials in all 50 states about their experiences in the 2000-01 flu season. In September 2004 we updated this work with information on the 2003-04 flu season, Centers for Disease Control and Prevention (CDC) activities, including its responses to our prior recommendations for prevention and control of influenza, and the status of this year's flu vaccine. To learn about pandemic planning efforts, we interviewed HHS officials in the National Vaccine Program Office and reviewed HHS's August 2004 draft "Pandemic Influenza Preparedness and Response Plan." We conducted all of our work in accordance with generally accepted government auditing standards.

In summary, challenges persist in ensuring an adequate and timely flu vaccine supply. The number of producers remains limited, and the potential for manufacturing problems such as those experienced in recent years is still present. If a manufacturer's production is affected, those providers who ordered vaccine from that manufacturer could experience shortages, while providers who received supplies from another manufacturer might have all the vaccine they need. This potential for imbalance is what creates situations in which some providers might not have enough vaccine for persons at highest risk, while other providers might have enough supply to hold mass-immunization clinics even for persons at lower risk for flu-related complications. To help limit the potential for such situations, CDC and others have taken such steps as adding flu vaccine to federal stockpiles and more aggressively monitoring the projected supply of vaccine. However, there is no system in place to ensure that seniors and others at high risk for complications receive flu vaccinations first when vaccine is in short supply.

[3]See "Related Products," at the end of this testimony, for a list of our earlier work related to flu vaccine and influenza pandemic planning.

HHS's draft "Pandemic Influenza Preparedness and Response Plan" provides a blueprint for the government's role but leaves some important decisions about the government's response unresolved. In addition to describing the federal role, responsibilities, and actions in collaboration with the states in responding to an influenza pandemic, the plan also provides planning guidance to state and local health departments and the health care system. The draft plan is comprehensive in scope, but it leaves decisions about the purchase, distribution, and administration of vaccines open for public comment and for the states to decide individually. In addition, the draft plan does not make recommendations for how population groups should be prioritized to receive vaccines in a pandemic. Difficulties encountered during the annual flu season with the purchase, distribution, and administration of flu vaccine highlight the importance of resolving these issues for pandemic preparedness.

Background

In almost every year an influenza virus causes acute respiratory disease in epidemic proportions somewhere in the world. Influenza is more severe than some of the other viral respiratory infections, such as the common cold. Most people who get the flu recover completely in 1 to 2 weeks, but some develop serious and potentially life-threatening medical complications, such as pneumonia. People who are aged 65 and older, people of any age with chronic medical conditions, children younger than 2 years, and pregnant women are more likely to get severe complications from influenza than other people. Influenza and pneumonia rank as the fifth leading cause of death among persons aged 65 and older.

For the 2004-05 flu season, CDC is recommending that about 185 million Americans in these at-risk populations and other target groups receive the vaccine, which is the primary method for preventing influenza. Flu vaccine is generally widely available in a variety of settings, ranging from the usual physicians' offices, clinics, and hospitals to retail outlets such as drugstores and grocery stores, workplaces, and other convenience locations. Millions of individuals receive flu vaccinations through mass immunization campaigns in nonmedical settings, where organizations such as visiting nurse agencies under contract administer the vaccine.[4] It takes

[4]Data collected by states through the CDC Behavioral Risk Factor Surveillance System during 2002 indicate that among persons aged 18 years or older reporting receipt of flu vaccine, about two-thirds reported getting their last flu vaccination at a health care facility, such as a doctor's office, health center or health department, while about one-third reported getting vaccinated at a workplace, community center, store, or other location.

about 2 weeks after vaccination for antibodies to develop in the body and provide protection against influenza virus infection. CDC recommends October through November as the best time to get vaccinated because the flu season often starts in late November to December and peaks between late December and early March. However, if influenza activity peaks late, vaccination in December or later can still be beneficial.

Producing the influenza vaccine is a complex process that involves growing viruses in millions of fertilized chicken eggs. This process, which requires several steps, generally takes at least 6 to 8 months from January through August each year, so vaccine manufacturers must predict demand and decide on the number of doses to produce well before the onset of the flu season. Each year's vaccine is made up of three different strains of influenza viruses, and, typically, each year one or two of the strains is changed to better protect against the strains that are likely to be circulating during the coming flu season. The Food and Drug Administration (FDA) and its advisory committee decide which strains to include based on CDC surveillance data, and FDA also licenses and regulates the manufacturers that produce the vaccine.

In a typical year, manufacturers make flu vaccine available before the optimal fall season for administering flu vaccine. Currently, two manufacturers—one in the United States and one in the United Kingdom—produce over 95 percent of the vaccine used in the United States.[5] According to CDC officials, for the 2002-03 flu season, manufacturers produced about 95 million doses of vaccine, of which about 83 million doses were used and 12 million doses went unused. Production for the 2003-04 flu season was based on the previous year's demand and was about 87 million doses. For the 2004-05 season, CDC estimates that about 100 million doses will be available.

Currently, flu vaccine production and distribution are largely private-sector responsibilities. Like other pharmaceutical products, flu vaccine is sold to thousands of purchasers by manufacturers, numerous medical supply distributors, and other resellers such as pharmacies. These purchasers provide flu vaccinations at physicians' offices, public health clinics, nursing homes, and less traditional locations such as workplaces

[5]A third U.S. manufacturer produces a flu vaccine that is given by nasal spray and is only approved for healthy persons aged 5 through 49 years. According to CDC, this manufacturer is likely to supply about 1.5 million doses in the 2004-05 season.

and various retail outlets. Most influenza vaccine distribution and administration are accomplished within the private sector, with relatively small amounts of vaccine purchased and distributed by CDC or by state and local health departments.

HHS also has a role in planning to prepare for and respond to an influenza pandemic. Planning is key to being prepared for and mitigating the negative effects of the next influenza pandemic, including major illness, death, economic loss, and social disruption. A national pandemic influenza plan was first developed in 1978 and was revised in 1983. In 1993, efforts to revise the national plan were initiated, and these efforts picked up momentum in the late 1990s. In August 2004, HHS released a draft plan for comment entitled, "Pandemic Influenza Preparedness and Response Plan."

To foster state and local pandemic planning and preparedness, CDC first issued draft interim planning guidance to states in 1997 and posted guidance on its Web site for state and local health departments in 2001. Since that time, states have been preparing pandemic response plans, and many are integrating these plans with existing state plans to respond to public health emergencies such as natural disasters and bioterrorist attacks.

Challenges Exist in Ensuring an Adequate and Timely Flu Vaccine Supply

Ensuring an adequate and timely supply of vaccine is a difficult task. It has become even more difficult because there are few manufacturers. Problems at one or more manufacturers can significantly upset the traditional fall delivery of influenza vaccine. These problems, in turn, can create variability in who has ready access to the vaccine.

Matching flu vaccine supply and demand is a challenge because the available supply and demand for vaccine can vary from month to month and year to year. For example,

- In 2000-01, when a substantial proportion of flu vaccine was distributed much later than usual due to manufacturing difficulties, temporary shortages in the prime period for vaccinations were followed by decreased demand as additional vaccine became available later in the year. Despite efforts by CDC and others to encourage people to seek flu vaccinations later in the season, providers still reported a drop in demand in December. The light flu season in 2000-01, which had relatively low influenza mortality, probably also contributed to the lack of interest. As a result of the waning demand that year, manufacturers and distributors reported having more vaccine than they could sell. In addition, some physicians'

offices, employee health clinics, and other organizations that administered flu shots reported having unused doses in December and later.

- For the 2003-04 flu season, shortages of vaccine have been attributed to an earlier than expected and more severe flu season and to higher than normal demand, likely resulting from media coverage of pediatric deaths associated with influenza. According to CDC officials, this increased demand occurred in a year in which manufacturers had produced about the same number of doses as in the previous season and that supply was not adequate to meet the demand.

If production problems delay the availability of vaccine in a given year, the timing for an individual provider to obtain flu vaccine may depend on which manufacturer's vaccine it ordered. This happened in the 2000-01 season, and it could happen again. This year, one of the two major manufacturers recently announced a delay in its shipments of vaccine. On August 26, 2004, one manufacturer announced that release of its flu vaccine would be delayed because of production problems related to sterility of a small number of doses at its manufacturing facility. The company stated that it expected to deliver between 46 million and 48 million doses to the U.S. market beginning in October, and CDC issued a notice on September 24, 2004, stating that some delays might occur for customers receiving this manufacturer's vaccine. Those customers may receive their vaccine later than those who ordered from the other manufacturer, which reported sending its vaccine on schedule beginning in August and September. As a result, one provider could hold vaccination clinics in early October that would be available to anyone who wants a flu shot, while another provider would not yet have any vaccine for its high-risk patients.

Shortages of flu vaccine can result in temporary spikes in the price of vaccine. When vaccine supply is limited relative to public demand for flu shots, distributors and others who have supplies of the vaccine have the ability—and the economic incentive—to sell their supplies to the highest bidders rather than filling lower-priced orders they had already received. When there was a delay and temporary shortage of vaccine in 2000, those who purchased vaccine that fall—because their earlier orders had been cancelled, reduced, or delayed, or because they simply ordered later—found themselves paying much higher prices. For example, one physician's practice ordered flu vaccine from a supplier in April 2000 at $2.87 per dose. When none of that vaccine had arrived by November 1, the practice placed three smaller orders in November with a different supplier at the escalating prices of $8.80, $10.80, and $12.80 per dose. On December 1, the

practice ordered more vaccine from a third supplier at $10.80 per dose. The four more expensive orders were delivered immediately, before any vaccine had been received from the original April order.

Our work has also found that there is no mechanism in place to ensure distribution of flu vaccine to high-risk individuals before others when the vaccine is in short supply. When the supply was not sufficient in the fall of 2000, focusing distribution on high-risk individuals was difficult because all types of providers served at least some high-risk individuals. Some physicians and public health officials were upset when their local grocery stores, for example, were offering flu shots to everyone when they, the health care providers, were unable to obtain vaccine for their high-risk patients. Many physicians reported that they felt they did not receive priority for vaccine delivery, even though about two-thirds of seniors—one of the largest high-risk groups—generally get their flu shots in medical offices.[6] In our follow-up work, we found no indication that the situation would be different if there was a shortage today.

This raises the question of what more can be done to better prepare for possible vaccine delays and shortages in the future. Because flu vaccine production and distribution largely are private-sector responsibilities, options are somewhat limited. While CDC can recommend and encourage providers to immunize high-risk patients first, it does not have control over the distribution of vaccine, other than the small amount that is distributed through public health departments.

Although HHS has limited authority to directly control flu vaccine production and distribution,[7] it undertook several initiatives following the 2000-01 flu season. More specifically, CDC has taken actions that may

[6]Data collected by states through the CDC Behavioral Risk Factor Surveillance System during 2002 indicated that among persons aged 65 years or older reporting receipt of influenza vaccine, about 58 percent reported receiving their last influenza vaccination at physicians' offices and health maintenance organizations; followed by clinics or health centers (12 percent); stores (8 percent); community centers (6 percent); health departments (6 percent); other locations (5 percent); hospitals (4 percent); and workplaces (2 percent). Percentages do not add to 100 due to rounding.

[7]Under the Federal Food Drug and Cosmetic Act, FDA ensures compliance with good manufacturing practice and has limited authority to regulate the resale of prescription drugs, including influenza vaccine, that have been purchased by health care entities such as public or private hospitals. This authority would not extend to resale of the vaccine for emergency medical reasons. The term health care entity does not include wholesale distributors. CDC has a role in encouraging appropriate public health actions.

encourage manufacturers to supply more vaccine because the action could lead to increased or more stable demand for flu vaccines. Actions taken by CDC and its advisory committee include the following:

- Extending the optimal period for getting a flu vaccination until the end of November, to encourage more people to get vaccinations later in the season.
- Expanding the target population to include children aged 6 through 23 months and all persons who take care of children aged 0 to 23 months.
- Including the flu vaccine in the Vaccines for Children (VFC) stockpile to help improve flu vaccine supply. For 2004, CDC has contracted for a stockpile of approximately 4.5 million doses of flu vaccine through its VFC authority.
- Beginning an annual assessment of the projected vaccine supply, and making a determination if vaccination should proceed for all persons or if a tiered approach should be used, targeting limited vaccine supplies to seniors and other high-risk individuals first.

For both last season and the upcoming flu season, CDC announced that it did not envision any need for a tiered approach. For the 2004-05 flu season, CDC issued a notice on September 24 recommending that vaccination proceed for all recommended persons as soon as vaccine is available.

HHS's Draft Pandemic Influenza Plan Defines Roles and Responsibilities but Leaves Some Important Issues Unresolved

HHS's draft pandemic influenza plan describes federal roles and responsibilities in responding to an influenza pandemic and provides planning guidance to state and local health departments and the health care system. Although the draft plan is comprehensive in scope, it leaves some important decisions about the purchase, distribution, and administration of vaccines unresolved. In addition, the draft plan does not make recommendations for how population groups should be prioritized to receive vaccines in a pandemic. Consequently, states are left to make their own decisions, potentially compromising the timing and adequacy of a response to an influenza pandemic.

Draft Plan Defines Roles and Responsibilities

HHS's draft pandemic influenza plan describes HHS's role in coordinating a national response to an influenza pandemic and provides guidance and tools to promote pandemic preparedness planning and coordination at federal, state, and local levels, including both the public and the private sectors. Pandemic influenza response activities are outlined by the different phases of a pandemic.[8] The draft plan also provides technical background information on preparedness and response activities such as vaccine development and production.

The draft plan acknowledges that states and local areas have important roles in the national response to a pandemic. To facilitate the state and local response, the draft plan provides guidance for state and local health departments and the health care system. The draft plan states that planning for an influenza pandemic will build on HHS-supported efforts to prepare for other public health emergencies such as infectious disease outbreaks, bioterrorist events, or natural disasters, and provides important guidance on areas specific to an influenza pandemic, including disease surveillance, delivery of vaccine and other medications, and communication. According to the Council of State and Territorial Epidemiologists, currently 11 states have pandemic influenza plans. Six of these states have final plans, and five states have draft plans.[9]

According to the draft plan, federal agencies are taking steps to ensure and expand influenza vaccine production capacity; increase influenza vaccination use; stockpile influenza medications; enhance U.S. and global disease detection and surveillance infrastructures; expand influenza-related research; support public health planning and laboratory capacity; and improve health care system readiness at the community level. Although most of these activities have not been targeted specifically to pandemic planning, according to HHS officials, spending in these areas will help prepare for the next influenza pandemic. The draft plan also encourages states to allocate funding from the CDC Bioterrorism

[8]HHS describes five phases of a pandemic. In phase 1, there is an outbreak in one country, confirmation of efficient person-to-person transmission, and serious morbidity and mortality. In phase 2, there are regional outbreaks with global disease spread. Phase 3 is the end of the first pandemic wave; phase 4 refers to a second seasonal wave. In phase 5, the pandemic ends as population immunity has increased.

[9]California, Florida, Indiana, Maryland, Minnesota, and New Jersey have final plans, and Massachusetts, New Hampshire, South Carolina, Tennessee, and Texas have draft plans.

Cooperative Agreement and 2004 Immunization Continuation Grants for pandemic preparedness planning.[10]

Draft Plan Leaves Many Important Issues Unresolved, Making It Difficult for States to Plan

Although HHS's draft pandemic influenza plan is comprehensive in scope, it leaves many important decisions about the purchase, distribution, and administration of vaccines unresolved. These decisions include determining the public- versus the private-sector roles in the purchase and distribution of vaccines; the division of responsibility between the federal government and the states for vaccine distribution; and how population groups will be prioritized and targeted to receive limited supplies of vaccines. As we have stated previously, until these key decisions are made, states will find it difficult to plan, and the timeliness and adequacy of response efforts may be compromised.

The draft plan does not establish a definitive federal role in the purchasing and distribution of vaccine. Instead, HHS provides options for vaccine purchase and distribution that include public-sector purchase and distribution of all pandemic influenza vaccine; a mixed public-private system where public-sector supply may be targeted to specific priority groups; and maintenance of the current largely private system. Currently, approximately 85 percent of the influenza vaccine produced for annual outbreaks is purchased by the private sector, and a majority of the annual vaccinations are also delivered by the private sector. HHS states in the draft plan that such a distribution method may not be optimal in a pandemic.

Furthermore, the draft plan delegates to the states responsibility for distribution of vaccine. The lack of a clearly defined federal role in distribution complicates pandemic planning for the states. Among the current state pandemic influenza plans, there is no consistency in terms of their procurement and distribution of vaccine and the relative role of the federal government. States also approach annual vaccine procurement and distribution differently. Approximately half the states handle procurement and distribution of the influenza vaccine through the state health agency. The remainder either operate through a third-party contractor for distribution to providers or use a combination of these two approaches.

[10]Under the CDC's Public Health Preparedness and Response for Bioterrorism Program, all 50 states, the District of Columbia, the country's largest municipalities, and territories receive funding to complete specific activities designed to build public health and health care capacities.

In 2003 we reported that state officials were concerned that there were no national recommendations for how population groups should be prioritized to receive vaccines. Identifying priority populations from among high-risk groups and essential health care and emergency personnel is likely to be a controversial issue. The draft plan does not identify priority groups, but HHS indicates that it has separately developed an initial list of suggested priority groups and is soliciting public comment on this list. The draft pandemic plan instructs the states to prioritize the persons receiving the initial doses of vaccine and indicates that as information about the severity of the virus becomes available, recommendations will be formulated at the national level. Prioritization will be an iterative process and will be tied to vaccine availability and the progression of the pandemic. While recognizing that this is an iterative process, state officials have consistently told us that a lack of detailed guidance makes it difficult for states to plan for the use of limited supplies of vaccine.

Concluding Observations

Ensuring an adequate and timely supply of vaccine to protect seniors and others from influenza and flu-related complications continues to be challenging. Only two manufacturers currently produce flu vaccine for seniors and others at high risk for flu-related complications, and manufacturing problems experienced in recent years illustrate the fragility of the current methods of production. Despite efforts by CDC and others, there remains no system to ensure that persons at high risk for complications receive flu vaccine first when vaccine is in short supply.

These influenza vaccine supply and distribution problems may become especially acute in a pandemic. We acknowledge the need for flexibility in planning because many aspects of an influenza pandemic cannot be known in advance. However, the absence of more detail in HHS's draft plan creates uncertainty for the states regarding how to plan for the use of limited supplies of vaccine. Until decisions are made about vaccine purchase, distribution, and administration, and priority populations are designated, states will not be able to develop strategies consistent with federal priorities.

Agency Comments

Officials from CDC provided technical comments that we incorporated as appropriate.

Mr. Chairman, this concludes my statement. I would be happy to answer any questions you or other Members of the Committee may have.

Contact and Staff Acknowledgments

For further information about this testimony, please contact Janet Heinrich at (202) 512-7119. Gigi Barsoum, Anne Dievler, Martin Gahart, Jennifer Major, Roseanne Price, and Kim Yamane also made key contributions to this statement.

Related GAO Products

SARS Outbreak: Improvements to Public Health Capacity Are Needed for Responding to Bioterrorism and Emerging Infectious Diseases. GAO-03-769T, Washington, D.C.: May 7, 2003.

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The CHAIRMAN. Janet, thank you very much. Now let us turn to you, Carol. Please proceed.

STATEMENT OF CAROL M. MOEHRLE, DISTRICT DIRECTOR, NORTH CENTRAL DISTRICT HEALTH DEPARTMENT, LEWISTON, ID

Ms. MOEHRLE. Thank you. Good morning, Mr. Chair. It is my pleasure to address you today with the prospective of a local public health department as it relates to flu vaccinations and the elderly. I am also honored to represent the National Association of County and City Health Officials, NACCHO, our national organization representing the nation's nearly 3,000 local health departments.

As we all know, the old adage, says, "It's at the local level where the rubber meets the road," when we talk about flu vaccine, it is also the local level where that needle finally meets the arm of each of those receiving that vaccine.

I am particularly proud to share with you some of our collaboration that our health district has been doing with the Idaho Commission on Aging. Our health district, along with two others in the state, have joined with the Commission on Aging to develop outreach to our senior citizens in our most rural areas of Idaho.

The public health districts are providing information and oftentimes flu vaccine clinics at the senior meal sites in these rural areas. The commission is helping us by identifying certain homebound seniors that are not able to attend these flu clinics and we are sending a public health nurse into those homes to give those seniors their vaccine.

This joint effort is to increase the flu vaccination rate amongst those very fragile, very elderly in our state of Idaho. However skilled we are at locating these high-risk individuals and administering the vaccine, we cannot achieve optimal protection for our communities unless the vaccines are available to us.

The nation's local public health departments have experienced distribution issues in four out of five of the last flu seasons. We do not yet know what challenges await this year, but we are hopeful that maybe we will not have to be as worried as we have been in the past.

In the five counties that my health district covers in north Idaho, we are already hearing flu concerns, and receiving questions, and dozens of phone calls each week from citizens wanting to know about the flu vaccine for this year. Will there be shortages? Will there be an ample amount?

I spoke with one elderly woman just recently who was quite distressed. She insisted that she get her vaccine first. She is elderly, has frail health concerns, and wanted to receive it before the lines start forming that oftentimes do in the clinics.

She was worried also about the safety of the vaccine given the most recent media telling us about some of the vaccine being recalled. She wanted to know if we had the good vaccine or the bad vaccine?

I reassured her that even though we were hoping that we would have ample doses, we were convinced that we would have enough to serve the population, and all the doses that we had were safe doses of vaccine. She did not leave that call very settled. She was

quite disturbed still that I would not just let her have her vaccine today when she called and that I could not give her more reassurance that she wanted.

Those are some of the calls that we are already receiving. It is clear to me that many elderly residents, do not trust the ability of the public health system to deliver the vaccine when they need it, where they need it.

We have a lot of work to do to rebuild that trust because of the last few years and the issues that have happened. Idaho also experienced a flu shortage last year, as many of the health departments in our nation did.

We didn't receive the full amount of vaccine as that we ordered. We knew that we would run out. So we early on started prioritizing who the vaccine would be given to, and we used the CDC's guidelines for the high risk population. Many of the people that we customarily give flu vaccine to were quite disturbed and panicked that they were not among the highest risk that we were giving the vaccine to.

There was much emotion, confusion and even some anger in our communities that they could not receive this. Some people were so upset that they offered to pay more just so they could get a dose of vaccine.

During some of the clinics that we held, we were actually turning some people away that were not qualified in the high risk categories, only to find out that they showed up for the next clinic with made-up diseases so that they would then be able to receive their vaccine.

This pains me greatly that we have placed people in a situation where they have to lie about their health concerns in order to be amongst that high risk population when we have people that want to do the responsible thing to receive their flu vaccine.

It also demonstrates some of the most critical concerns we have about the supply. We do not believe that anyone has a clear understanding of the reason for the supply and distribution problems that we have seen in the recent years.

Every entity that gives flu shots, whether it is the large chain stores, the physicians or public health, we all order the vaccine from the same distributors and wholesalers. There does not seem to be a discernable rhyme or reason why some who place orders receive it early and in a full amount while others receive partial shipments sporadically throughout the flu season.

Two years ago, a local nursing home called me at the health department and said, "It is flu season, I have no vaccine." This was very concerning, a nursing home to call and not have received vaccine yet. I made more calls to other nursing homes and our senior living centers in our five counties, and lo and behold, we had others, other nursing homes that did not have flu vaccine.

We called a meeting with our local medical community. We had physicians and healthcare providers arrive and voluntarily turned over doses of vaccine to Public Health so we could redistribute to the most at-risk, our elderly seniors in those living centers.

The cooperative spirit that we had with our medical community helped us to address this distribution problem successfully, but on the contrary, we had two large chain stores that had received their

full amount of vaccine early on. When asked to come to the table, they said that they were continuing to give the vaccine to anyone who walked through their stores and could not spare to give this to the public health when we thought it needed to be distributed elsewhere.

In times of shortage, we all need to be working together with the same guidelines and the same rules as we use the vaccine very responsibly. Public Health urges stronger Federal leadership to bring all the parties together to find ways to rationalize the current chaotic distribution system, and to collaborate to assure optimal distribution of all the flu vaccine.

If a nightmare of a flu pandemic ever arrives, we believe that the Federal Government will need to step in to take a strong hand in vaccine distribution because only optimal distribution will be essential to stemming outbreaks and to saving lives.

Senator Craig, thank you for holding this hearing and for your support of public health. I will stand for questions.

[The prepared statement of Ms. Moehrle follows:]

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NATIONAL
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COUNTY & CITY
HEALTH OFFICIALS

Statement of

Carol M. Moehrle

Director, North Central District Health Department

Lewiston, Idaho

On behalf of the

National Association of County and City Health Officials

Before the Special Committee on Aging

United States Senate

Hearing on "Combating the Flu: Keeping Seniors Alive"

September 28, 2004

It is my pleasure, Chairman Craig and distinguished Senators, to address you today concerning the perspective of local public health departments on flu vaccination for the elderly. I am honored to represent the National Association of County and City Health Officials (NACCHO), the organization representing the nation's nearly 3000 local public health departments.

As you know, it is at the local level where the rubber meets the road and the shot meets the arm. Local health departments play essential roles in preventing cases of influenza. First, we organize and conduct flu immunization clinics. Second, we monitor flu immunization rates in our communities and work with our community partners to get flu shots to those most in need, particularly the elderly. Third, we address vaccine shortages when they occur, working to gain voluntary cooperation from entities that have vaccine supplies to reallocate vaccine to persons most at risk from influenza.

Local health departments have many decades of experience in immunization, going back to the days when polio vaccine was first developed. We have developed many ingenious strategies for getting flu shots to the community, particularly to those who are most vulnerable. We know that the easier we can make it for people to get their shots, the more likely it is that they will. We run public information campaigns and we go into the community as much as we can to administer shots. We work with private physicians, clinics and hospitals to encourage them to offer flu vaccine to every elderly person that they see, even if the person is visiting for other reasons. Some agencies are organizing "drive-through" flu vaccination clinics, where people need not even leave their cars to receive a shot.

I am particularly proud of my agency's collaboration with the Idaho Commission on Aging. Our Health District, which covers five counties in North Idaho, and two other Health Districts covering 14 other counties, have joined with the Idaho Commission on Aging to develop flu vaccine outreach to the senior populations in some of the most rural areas of Idaho. We are working with the Commission to provide flu information and vaccinations at rural senior meal sites. Commission staff are helping to identify the

homebound elderly and the public health agencies then send nurses to their homes to vaccinate them. In this way, we are increasing flu vaccination rates among the elderly, a population that is most at risk for complications from influenza.

However skilled we are at locating high risk individuals and administering vaccine, we cannot achieve optimal protection for our communities unless vaccines are available to us. The nation's local health departments have experienced shortages of flu vaccine in four of the last five flu seasons. We do not yet know what challenges await us in the upcoming season, but we are worried.

In the five counties that my Health District covers in North Idaho, residents have already begun asking how to get their flu shots. They are fearful that we will have a shortage this season like we have had in the past. We have received many dozens of calls. I spoke with one elderly woman recently who was close to a state of panic. She insisted that she should be among the first to receive her flu vaccination, due to her age and frail health, because she was afraid about what might happen to her if she got sick from the flu. Moreover, she was greatly worried about the safety of vaccines, due to the recent press coverage about possibly tainted lots of vaccine. She demanded to receive the "good" vaccine, not the "bad" vaccine. As much as I reassured her that we expected to receive all the doses of vaccine that we needed and that it would all be safe, she remained distraught. It is clear to me that many of our elderly residents don't trust the ability of the public health system to deliver the flu vaccines that they need, when they need it. We all have work to do to rebuild that trust.

On a national level, NACCHO began systematically monitoring local problems with flu vaccine supply and distribution last year. In early December, 2003, the nation was hearing the news about childhood deaths from flu. As public demand for vaccine escalated, CDC, physicians, and manufacturers were all advising people to contact their local health departments to get a flu shot. By December 10, 2003, 71% of a large, diverse sample of local health departments reported that they had no flu vaccine in inventory. They could not get any more vaccine from distributors and none of their neighbors had any, either. Where vaccine was available, health departments began to ration it according to the guidelines of CDC's Advisory Committee on Immunization Practices.

Idaho experienced last year's flu shortage and we took steps similar to those taken by public health departments nationally. We did not receive the full amount of vaccine that we ordered and our suppliers told us they could not obtain more. We knew that we would run out of vaccine so we began prioritizing the vaccine for the high risk groups early, using CDC's guidelines. Many people that we customarily serve were truly panicked about not being able to receive flu vaccine. There was much emotion and anger in our communities. Some people, upset that they didn't fit the high risk definition, offered to pay more for a dose, and we had instances where people told us they had extreme diseases in order to obtain the vaccine. It pains us greatly to have placed people in the situation of needing to lie about their health in order to obtain vaccine. .

This demonstrates our most critical continuing concern about flu vaccine supply. Even if manufacturers are able to provide enough vaccine, there is no guarantee that the most vulnerable people, the elderly, will be able to receive it. We do not believe that anyone has a clear understanding of the reasons for the supply and distribution problems that have arisen so consistently in recent years. Every entity that gives flu shots, from large chain stores to individual physicians to health departments, orders its vaccine from wholesalers and distributors or from the manufacturers directly. There is no discernible rhyme or reason why some who place orders receive ample supplies early, and why some must wait, or receive partial shipments over a period of time.

At best, this level of uncertainty hampers our ability to make and carry through firm plans to vaccinate the elderly in our communities. As we are seeing in Idaho, the bad experiences of one season carry over into the next by causing great public concern.

At worst, the uncertainty about vaccine supply prevents the nation's public health system from filling its most essential role of reducing the toll of flu by getting vaccine to the most vulnerable. At times when vaccine supply unexpectedly becomes low or spotty, public health authorities have missed an opportunity to use earlier existing supplies judiciously by giving priority to the elderly and other high risk groups. There have been instances where large chain stores, who vaccinate everyone who comes through their doors, have ample supplies, while health departments and nursing homes who serve the frail elderly have little or none.

This happened in northern Idaho two years ago, when we had a shortage. A local nursing home called the health department to tell us that it had not received any flu vaccine. We then made calls to the other nursing homes and senior living centers to check on the status of their vaccine supplies. Several of them had not received any vaccine at the beginning of the flu season. Our public health department then called a meeting with our local medical community. Physicians and other health providers who had received vaccine agreed that they would offer some doses to our agency to distribute to the nursing homes in need. This cooperative spirit in the medical community is critical to our ability to address problems with flu vaccine distribution successfully. By contrast, two large chain stores had plenty of vaccine, but they informed us that they would be moving ahead with their plan to vaccinate anyone who came to their stores and would not consider sharing with the rest of the community. We do not believe that vaccine purchasers who find a way to get vaccine supplies early should be able to use it this irresponsibly in times of shortage.

The last few years have demonstrated how vulnerable the vaccine supply is to unpredictable disruptions. At the local level, uncertainties and shortages have become more the norm than the exception. Local and state public health departments have begun developing systems to monitor and reallocate vaccine supplies when shortages occur. This requires a large expenditure of time on identifying which physicians, hospitals, health centers, and nursing homes have vaccine and which are in need. These providers are asked to report doses on hand and to voluntarily return excess doses to a depository, which then redistributes vaccine to those who need more doses. These activities can help mitigate supply imbalances when the overall supply is adequate, but we have a long way to go before they are functioning with full effectiveness in every state and locality.

It is essential that the nation's public health system, vaccine manufacturers and distributors, and health care providers, collaborate more closely to assure optimal distribution of flu vaccine. We urge stronger, greater federal leadership to bring these parties together and find ways to rationalize the current chaotic distribution system. If the nightmare of a flu pandemic ever arrives, we believe that the federal government will

need to step in to take a strong hand in vaccine distribution, because optimal distribution will then be essential to stem outbreaks and save lives.

NACCHO is happy to support the Flu Protection Act of 2004. It includes many steps that we believe will help improve flu vaccination rates. However, we also recommend that the bill give greater attention to the roles of local public health departments in flu vaccination and we will be happy to work with you to achieve this.

Thank you for holding this hearing and for your support of public health. I'll be happy to respond to any questions you may have.

The CHAIRMAN. Carol, thank you very much. Now let us turn to Howard Pien, president and CEO of Chiron Corporation. Howard, please proceed.

STATEMENT OF HOWARD PIEN, CEO AND PRESIDENT, CHIRON CORPORATION, EMERYVILLE, CA

Mr. PIEN. Mr. Chairman, thank you for the opportunity to appear at this hearing. Today I would like to focus on three key messages. First, Chiron reiterates our expectation that we can deliver between 46 and 48 million doses of flu vaccine this season as we previously announced. We expect to make an announcement on our shipment plans in the next few days. We profoundly regret that we have caused uncertainties in this year's flu vaccine supply. However, in considering all of the dimensions of our responsibility as a vaccine supplier, we ultimately place the heaviest weight on the preservation of the trust of Americans that when they get the flu shot, the product is safe.

This is the reason that we have been deliberate, thorough and extremely careful. The issues we encountered this year do highlight some of the important and valuable principles.

First, the system in place to test flu vaccine does work. The problem was identified before release of a single dose of the vaccine to the public. So to Ms. Moehrle's comment and phone call that she got, there is no bad vaccine. There is not going to be a recall because we will not release a single dose of the vaccine, until we are certain that the quality issues have been put to bed.

But we also learned that when there is unexpected disruption in supply, timely and transparent communication is most important. We have benefited enormously from the guidance and the advice of the men and women serving the public health interest at the FDA, the CDC, and the other parts of Health and Human Services.

We pledge always to be open in our communication and to help ensure that there are concerted efforts to coordinate communication to the public at large. Without that kind of communication, there is every risk of misinformation, possible panic, and erosion of public confidence in vaccines.

My second message today is that while significant advances have been made in increasing immunization rates in older Americans, greater enhancements are possible, particularly for individuals between 50 and 64 years of age and healthy adults in close contact with people at high risk. The threat of flu to public health makes the enhancement of vaccination rates one of the clearest and most accessible ways to improve the health of Americans, and we applaud this committee in holding this hearing.

Progress has been made in raising flu coverage rates, but as Dr. Ostroff pointed out, we still have a long way to go. Only 65 percent of the high-risk population over 65 are immunized. It is estimated that only 34 percent of those between the age of 50 and 64 have received vaccine, and the immunization of healthcare workers is less than 40 percent as we heard.

Chiron believes that the following are paramount in importance to expand the rate of immunization. Education is critical. Public/private partnerships, such as that of National Influenza Vaccine Summit, need to undertake substantial and innovative efforts to

raise flu immunization coverage rates in any individuals over the age of 50 as well as their contacts. We can and we should reduce the disparities between geographic areas and between racial and ethnic groups.

Also, vitally important is a recommendation for universal immunization. Expanding today's recommendations to cover more than the 60 percent of the population currently covered will enhance our pandemic readiness as a nation. The Canadian province of Ontario has already done this and so can the United States.

Finally, we need better incentives for immunization when it comes to flu and its terrible complications, the best medicine is preventive medicine. Therefore the best health economic policy is for the CMS to continue to encourage physicians to actively immunize against flu by setting adequate administration fees and reimbursement rates.

My third message is that over the past year, collaboration between the public sector and industry has led to significant progress in both flu vaccine supply and pandemic preparedness. It is imperative that these efforts are sustained because they have led to improvements already and we should maintain the momentum.

Here are some of the examples:

The CDC has worked with flu vaccine manufacturers to establish a reserve of over four million doses to be delivered at the end of the flu season. Chiron will deliver two million doses to this buffer stock.

The National Institute of Allergy and Infectious Disease with the leadership that we have grown to expect from the NIH has supported the production and testing of candidate vaccines against pandemic strains of avian flu that was described by Dr. McInnes. Chiron is manufacturing pilot lots of H5N1 and H9N2 vaccine to enable NIH's evaluation.

A draft pandemic influenza preparedness and response plan was recently published by the National Vaccine Program Office. The document will stimulate discussion and set priorities to enhance our preparedness including distribution against the pandemic threat. Chiron pledges to contribute to this important discussion.

Our recommendation on pandemic readiness has already been incorporated in our written testimony. Briefly, the tenets are:

Educating the public to increase the uptake of flu vaccine in the aged and their contacts and caregivers;

Increasing research and development to enable higher certainty of sufficient pandemic vaccine supply;

Proactively removing the obstacles in pandemic vaccine production including indemnification to the suppliers and well-defined government purchase, contractual arrangements and distribution plans.

Finally, and perhaps most importantly, sustaining the political will to address the threat that flu represents to America's health beyond this flu season and beyond this congressional session.

In summary, on behalf of Chiron Corporation, I respectfully submit the following thoughts:

First, Chiron expects to deliver between 46 to 48 million doses of the vaccine this season. Second, increasing the willingness of the public to be immunized this season and in the future is critical.

Public-private partnerships are the best mechanisms for maintaining the momentum. Third, the public sector and the industry have the opportunity in the next Congress to build on progress that has already occurred this year in both vaccine supply and in pandemic preparedness. We should seize on that spirit of collaboration with zeal.

Thank you, Mr. Chairman, for the opportunity to represent Chiron's views.

[The prepared statement of Mr. Pien follows:]

CHIRON

Statement Presented To

Committee on Aging

United States Senate

By Howard Pien

President and CEO

Chiron Corporation

September 28, 2004

Introduction

Mr. Chairman, Members of the Committee: Thank you for the opportunity to provide a statement to the Committee on Aging at today's hearing. I am Howard Pien, president and CEO of Chiron Corporation, a global biotechnology company headquartered in Emeryville, California with 2003 revenues of $1.75 billion. Founded in California in 1981, Chiron is composed of three business units: BioPharmaceuticals, Blood Testing and Vaccines. Chiron is dedicated to research and innovation addressing global public health challenges. Through Chiron's breakthrough research discoveries in the fields of hepatitis B virus, human immunodeficiency virus and hepatitis C virus, millions of potentially fatal infections have been prevented.

Overview of Chiron

Chiron is the fifth-largest vaccines producer in the world, with sales of $678 million in 2003. Chiron Vaccines produces pediatric and adult vaccines to prevent life-threatening illnesses. These vaccines, which are sold throughout the world, have protected millions of people globally from *N. Meningitidis* Group C, polio, measles and other potentially fatal diseases. Chiron is a leading supplier of oral polio vaccine, producing more than 800 million doses annually to support global polio eradication efforts. Our rich heritage in vaccines is traced to the three European manufacturers Chiron has acquired over the past two decades, all of which were founded 100 or more years ago. The company has production facilities in Liverpool, United Kingdom; Siena, Italy; Marburg, Germany; and Ankleshwar, India; and it carries out research in Siena, Marburg and Emeryville. Chiron has a successful record of product development, including the launch of the first recombinant vaccine against pertussis, the first adjuvanted influenza vaccine and a conjugate vaccine against *N. Meningitidis* Group C.

Chiron currently has two vaccines licensed in the United States: Fluvirin® influenza vaccine, one of only two injectable influenza vaccines approved by the U.S. Food and Drug Administration (FDA), and RabAvert® rabies vaccine, approved by the FDA in 1997. Fluvirin® is indicated for immunization against the influenza vaccine strains contained in the vaccine for persons of 4 years of age and older. Chiron also supplies diphtheria and tetanus (DT) concentrate to GlaxoSmithKline for use in its DT-containing vaccines licensed by the FDA.[1] In addition, Chiron has initiated Phase III studies in the United States with the aim of licensing its conjugate vaccine against *N. Meningitidis* Group C, Menjugate®.[2]

Chiron and Influenza Vaccines

Chiron's $878 million acquisition of PowderJect Pharmaceuticals and its influenza vaccine Fluvirin in July 2003 represents a major commitment to ensuring that an adequate supply of vaccine is available to meet the needs of the United States. The principle driver for the acquisition was Fluvirin, produced at the company's FDA-licensed facility in Liverpool. Approximately 90 percent of the production from the

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[1] Infanrix (DtaP) & Pediarix (DtaP-HepB-IPV)

[2] Menjugate® has been licensed in Europe via the Mutual Recognition Procedure and is also approved in other countries, including Canada and Australia.

facility is delivered to the United States, with most of the remainder going to the United Kingdom.

Prior to its acquisition of PowderJect, Chiron was the third-largest producer of influenza vaccines globally and the second-largest supplier of influenza vaccine outside the United States. Today, Chiron is the second-largest producer of influenza vaccines in the world, with production of approximately 85 million doses annually. Chiron produces influenza vaccines at its facilities in Liverpool, Marburg and Siena and offers a number of influenza vaccines.

The acquisition of PowderJect represented a change in strategy for Chiron. Prior to this event, Chiron was unable to commit the resources required to enter the U.S. influenza market. However, over the last few years, significant changes in the dynamics of the U.S. influenza market have occurred. The key changes are:

- The recommendations of the Advisory Committee on Immunization Practices (ACIP) on influenza immunization were broadened to include individuals between 50 and 64 years of age and healthy children between 6 and 23 months of age, significantly expanding the potential market for influenza vaccine.
- Pricing of influenza vaccines has reached a level that allows manufacturers to invest in maintaining facilities to meet FDA standards and in expanding manufacturing capacity in order to meet increased demand.
- Reimbursement rates for providing influenza injections have been increased to levels at which physicians are encouraged to proactively immunize patients.

These changes in market dynamics were key factors in Chiron's decision to acquire PowderJect and expand its strong presence in the influenza market to include the United States. The shift in dynamics has also had a significant impact on investment decisions and capacity. Over the past five years, investments of approximately $70 million in both primary (bulk) and secondary (fill/finish) manufacturing have been made to increase the production capacity of the Liverpool facility. This investment was reflected in the purchase price of PowderJect and it has resulted in a significant increase in the amount of Fluvirin® supplied to the United States. The amount of Fluvirin® supplied to the United States on an annual basis more than quadrupled from 12 million doses in 2000 to 46-48 million doses in 2004, in addition to a two million dose supply for the Centers for Disease Control and Prevention (CDC) strategic reserve.

Building on recent investments to increase manufacturing capacity at the Liverpool facility, Chiron is committing an additional $100 million dollars to replace its existing influenza bulk manufacturing facility with a new "state of the art" facility[3] to complement the secondary manufacturing facility opened in 1998. This commitment is being made to ensure that Chiron is in a position to continue to supply Fluvirin to the United States and to add incremental capacity until sufficient cell-culture production capacity is available to meet the market needs in the United States.

[3] A new fill/finish facility was completed a few years ago.

It should be recognized that changes in market dynamics, specifically the increase in price that has occurred over the past three years, have reversed the trend of decreasing manufacturing capacity. Producers are investing in capacity increases, upgrading facilities and licensing cutting-edge technologies for the U.S. market. Chiron manufacturing investments are not unique in the industry, suggesting that the growing U.S. influenza market is an important public health priority that the private sector must ensure is addressed. However, given the nature of biologics manufacturing there is inevitably a lag between the decision to invest and improved capacity as a result of that investment. The United States is only now beginning to see the impact of the positive changes in market dynamics that occurred a few years ago with regard to expanded investment in manufacturing capacity.

Influenza Vaccine Production

Currently, all influenza vaccines marketed in the United States are produced in embryonated hens' eggs from designated chicken flocks. Individual lots of each of the three virus strains are grown in the eggs and harvested. The harvested virus is inactivated (killed), purified and separated from the egg proteins, usually by high-speed ultra-centrifugation. The whole virus concentrates are then further purified and split (split vaccine) or purified, as for Fluvirin, such that the vaccine contains predominately only the hemagglutinin and neuraminidase virus coat proteins (surface antigen or sub-unit). The monovalent (single-strain) antigen lots are sterile-filtered and quality control and potency tested. The monovalent lots are then formulated into trivalent vaccine (following FDA release), filled into the final containers and packed. The final run of primary antigen production in eggs is usually completed by September to allow time for processing, FDA potency assignment, vaccine formulation, packaging, quality assurance release and shipping to have completed release of the product into the marketplace by October or November.

In addition to its conventional egg-based influenza vaccines, Chiron is pursuing development of a cell culture–based subunit influenza vaccine using the Madin-Darby Canine Kidney (MDCK) cell line. Chiron's influenza cell-culture research program has completed Phase II clinical trials, with licensure in Europe projected sometime during the latter half of the decade. A Chiron influenza cell-culture production facility for full-scale production of the vaccine exists in Marburg. Chiron has submitted an Investigational New Drug Application to the FDA and is committed to licensure of its influenza cell-culture vaccine in the United States.

While there do not appear to be significant clinical advantages to cell-culture vaccines as compared with the current egg-based vaccines in terms of safety and efficacy, the cell-culture production process offers several potential advantages. The overall process is more flexible and can be more easily adapted to increases in market demand. Additionally, the fermentation process is a closed system highly compliant with Good Manufacturing Practice (GMP).

In the event of an influenza pandemic, the cell-culture production process offers the promise of significant benefits compared to the conventional process, including:

- Cell culture production allows increased production capacity via faster initiation of continuous manufacture.
- Cell culture production is not dependent on a supply of eggs, which could be a key rate-limiting step in meeting an urgent public health crisis. Production can start at any time and can easily be expanded to full-year production.
- Cell culture production can reduce lead-time by six to eight weeks.
- Cell-culture production, unlike egg-based production, is a closed process that can be easily upgraded to Class III bio-safety standards that may be required for the management of a pandemic strain.
- Cell-culture production is suited to producing vaccines for influenza of avian origin, which will not grow on eggs without genetic modification.

Overview of Egg-Based Influenza Vaccine Production

Influenza vaccine usually contains three different influenza strains that are recommended by the World Health Organization (WHO) and the FDA. The WHO and the FDA select the influenza strains and industry's role in the public health partnership is to manufacture the designated product. From continuous surveillance by the WHO and the FDA, select strains to match the families of influenza viruses expected to be circulating each winter. The vaccine has a new composition each year, and the vaccine therefore cannot be stockpiled but must be made to order annually. In addition, influenza vaccine is a seasonal product, with the majority of immunizations occurring in the September-to-November time frame in the United States. If there is surplus vaccine that is unused at the end of the season, it cannot be reused the following year and must therefore be destroyed. The requirement for Southern Hemisphere influenza vaccine in the January to March season is comparatively small and usually of a different composition.

Vaccine manufacturers try to match annual supply and demand, ensuring enough doses are available to meet demand while avoiding wasteful destruction of unused vaccine at the end of the season. The inability to carry over inventory into the following season means that the margin of error is much smaller than for other vaccines. Forecasting demand accurately is complicated by the fact that it is not possible to assess the severity of the epidemic and then adjust production volumes; additional capacity cannot be added at short notice and must be planned at least one season in advance. In fact, almost all the influenza vaccine manufacturing is completed before the influenza season begins. The cycle time for vaccine production means that demand must be predicted based on historical data, without an indication of the severity of the current influenza epidemic.

Supply of Influenza Vaccine for the 2004/2005 Influenza Season

On August 26th, Chiron Vaccines announced that in conducting final internal release procedures for its Fluvirin® influenza virus vaccine, our quality systems identified a small number of lots that did not meet product sterility specifications. Chiron therefore announced that it had delayed releasing any Fluvirin® doses until it had completed

additional release tests, a process that will delay release until October. As of September 27th, it remains Chiron's expectation that between 46 million and 48 million Fluvirin® doses will be delivered to the U.S. market beginning in early October as compared to the 50 million doses projected in July. Since the original announcement Chiron has worked closely with key stakeholders[4] to keep them abreast of the status of the testing. The planned late-season delivery of 2 million Fluvirin doses for a national stockpile held by the U.S. Centers for Disease Control and Prevention (CDC), not included in the totals above, remains on schedule. The results of the tests are entirely in line with the company's expectations that the variance was confined to the initial scope identified. Following compilation and formal sign-off of the test data, Chiron expects to report its conclusions to regulatory authorities and, upon confirmation, proceed with releasing Fluvirin® to the U.S. market in early October.

As October and November are the primary months when influenza vaccine is given, the impact of the delay on the 2004-2005 influenza vaccination season should be minimal. Furthermore, as in past years, CDC urges continuation of Influenza vaccination into December and beyond if vaccine is available and therefore ample time will exist to immunize individuals at risk from the disease. Chiron is extremely proud of the dedication displayed by its staff in working continuously these past few weeks to develop and execute the formal retest program making possible the delivery of a safe and effective vaccine in time to for the influenza season.

It is important to note that the 46-48 million doses of Fluvirin® projected for delivery during the 2004 /05 influenza season represents an increase of more than 25% compared to the amount of influenza vaccine Chiron supplied to the United States last season. Overall, the CDC estimates that there will be roughly 100 million doses of influenza vaccine available[5] representing an increase of approximately 15% compared to the 87 million doses of influenza vaccine available last season. In addition, in response to the supply shortage that occurred last year, the CDC has worked with influenza vaccine manufacturers to establish a ***"strategic reserve"*** of over 4 million doses of influenza vaccine delivered in November and December. Chiron, as mentioned previously, will deliver two million doses to the late season stockpile. Chiron welcomed the opportunity to work collaboratively with the CDC to develop the program securing a strategic reserve that did not create the unintended consequence of detrimentally impacting the private market. Therefore, despite the delay in availability of Fluvirin®, it does not appear that there will be a shortage of influenza vaccine this season as manufacturers will be supplying the United States with 13 million doses more than last year.

The key challenge for the 2004/05 influenza season will most likely not be managing a supply shortage but, rather, ensuring that all of the doses of influenza vaccine produced end up in the arms of individuals. Last year a milestone was reached: The estimated 83 million Americans immunized represented the highest immunization rate ever for

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[4] Chiron has held regular updates on the supply situation via teleconference with representatives from the CDC, National Vaccine Program Office, Advisory Committee on Immunization Practice, American Academy of Family Practitioners, American Academy of Pediatrics and the American Medical Association

[5] Inactivated influenza vaccine and live-attenuated vaccine

influenza and almost all the injectable inactivated influenza vaccine was used. Prior to 2003, immunization rates had remained relatively static, and unused vaccine had to be destroyed. For example, it is estimated that approximately 12 million doses were destroyed in 2002. Therefore, despite the delay in availability of vaccine, ensuring that demand exists for the additional influenza vaccine available this season is crucial in the context of planned increased production capacity for future seasons. If demand this season remains static, or returns to levels seen in 2002, supply will again exceed demand. Depending on the magnitude of the shortfall in demand it may lead to a reduction in supply in future years as supply of the vaccine is closely aligned with projected demand based on historical trends. Influenza immunization stakeholders in both the public and private sector are working together on activities to reassure the general population about the availability of vaccine, encourage influenza immunization and attempt to extend the influenza immunization season into December.

In summary, as mentioned previously, 2003 represented the highest number of people ever immunized, and there is no guarantee that the same levels will be achieved in the event of a less severe epidemic or a public perception of a supply shortage. We should therefore not be complacent and assume that because excess demand existed in 2003, it will automatically spill over and absorb the additional 13 million doses that will be available this season.

Protection of the Aging Population Against Influenza

Vaccination of persons at risk from the complications of influenza is a key public health strategy in preventing morbidity and mortality in the United States. The influenza epidemic is an annual event, which was estimated during the 1990s to have caused an average of approximately 36,000 deaths annually and 114,000 hospitalizations in the United States with 90% of the mortality occurring in adults aged 65 years of age and older[6]. A more recent study has suggested that the rate of hospitalizations related to influenza may be even higher with over 200,000 hospitalizations occurring annually[7]. Over the last decade the United States has had success in raising immunization coverage rates for individuals above 65 years of age. Data analyzed from the Behavioral Risk Factor Surveillance System (BRFSS) in 1993 indicated that 50% of respondents reported having received influenza vaccine compared to 66% in 2002[8]. This represents significant progress but is still below the 90% goal set for non-institutionalized adults in the Healthy People 2010 Objectives[9] and has remained level since 1997[10]. Continued investment in patient education and ensuring access to vaccine will be required if coverage rates are to continue to increase for individuals 65 years of age and older. Achieving higher coverage rates will increase in importance over the next few years as influenza is expected to have an increasingly serious impact in the United States due to the aging population. Therefore

[6] Source: Morbidity & Mortality Weekly Report 2003, Vol. 52 RR8
[7] Source: *JAMA*. 2004;292:1333-1340
[8] Source: Morbidity and Mortality Report 1996, Vol 45 No 40; Morbidity and Mortality Report 2003, Vol 52 No 41
[9] Objective no 14.29 at www.health.gov/healthypeople/
[10] Source: Morbidity and Mortality Report 2003, Vol 52 No 41

having effective strategies in place to prevent the disease through immunization will become increasingly important if the burden of disease is not to increase.

In addition to strategies that increase awareness of the need for prevention and access to the vaccine, setting appropriate reimbursement rates for vaccine purchase and administration is important, particularly through Medicare. The majority of the population 65 years of age and older receive vaccine from their primary health care provider and therefore ensuring incentives are in place for providers to actively immunize patients is important. The increases in the administration rates in 2003 by the Centers for Medicare and Medicaid Services (CMS) by roughly 90% to between six and eight dollars from less than four dollars has served to encourage physicians to actively seek out immunization in their population.

In addition to adequate administration fees, maintaining reimbursement rates that accurately reflect the acquisition cost of influenza vaccine creates an incentive for physicians to acquire the vaccine. In recognition of this, the Senate provided leadership in crafting the Medicare Modernization Act to ensure that influenza vaccine would be reimbursed at 95 percent of the Average Wholesale Price (AWP) and, equally important, that the Center for Medicare and Medicaid Services (CMS) continue its current practice and update this reimbursement rate on a quarterly basis. We understand that CMS will be sending a Transmittal to the Medicare Carriers reflecting this policy by the end of the month. Any change to the current reimbursement system will have a negative impact on coverage rates if it leads to a reduction in reimbursement for physicians. By setting adequate reimbursement rates and administration fees CMS has created an incentive for physicians to actively immunize their elderly patients against influenza. Any future changes to MMA through legislation or regulation must not create a disincentive for physicians to actively immunize their patients.

Individuals aged between 50-64 years old are another population that benefit significantly from influenza immunization as this population has an increased prevalence of high-risk conditions. In 2000, approximately 42 million persons in the United States were aged 50–64 years, of whom 12 million (29%) had one or more high-risk medical conditions. In 2000 the Advisory Committee on Immunization Practices (ACIP) broadened the universal recommendations for influenza vaccine to include individuals between 50-64 years of age because of the prevalence of high-risk conditions in this group. Influenza vaccine was recommended for this entire age group to increase the low vaccination rates among persons in this age group with high-risk conditions. Age-based strategies are more successful in increasing vaccine coverage than patient-selection strategies based on medical conditions. In addition, individuals aged between 50 and 64 years without high-risk conditions also receive benefit from vaccination in the form of decreased rates of influenza illness, decreased work absenteeism, and reduced need for medical visits and medication. For example a reduction in the use of antibiotics to which antimicrobial resistance is an increasing problem. Furthermore, fifty is an age when other preventive services begin and therefore the timing is appropriate.

Despite the universal recommendation being in place for several seasons only 36% of respondents between 50-64 years of age in the 2002 BRFSS reported having received influenza vaccine during the previous 12 months, well below the level of respondents above 65 years of age. Significant efforts need to be invested in reaching this age group for the following reasons. First, as stated in the previous paragraph, roughly one third of the individuals in this age group are estimated suffer from conditions such as chronic disorders of the pulmonary or cardiovascular systems, including asthma and metabolic diseases such as diabetes that put them at higher risk of complications due to influenza. Second, in the longer term, achieving high influenza coverage rates in this age group will translate to future higher coverage rates in the 65 and older population. It is likely that an individual who is in the habit of getting an annual influenza vaccine is likely to continue to do so as they age.

Chiron believes that substantial and innovative efforts need to be undertaken to raise influenza immunization coverage rates in individuals aged 50 and above. Specific efforts should be targeted at reducing disparities between geographic areas and racial / ethnic groups. For example, coverage rates are lower for Hispanics and non-Hispanic blacks as compared to non-Hispanic whites[11]. The variation in influenza vaccine coverage observed among geographic areas suggests that opportunities exist to apply lessons from high coverage areas such as the New England States to raise rates in low coverage areas. These efforts can have the biggest impact through collaboration between the public and private sector. Chiron believes that key stakeholders (manufacturers, distributors, the public health community, providers and insurers) should form public private partnerships to address the following:

- Raising awareness of the immunization recommendations among the medical community and general population.
- Dispelling some of the myths about influenza vaccine that exist ***(I can get influenza from the vaccine)***
- Encouraging immunization by highlighting the benefits of immunization and developing innovative programs for facilitating access to the vaccine.
- Extending the immunization season into December to ensure all doses are used and to potentially increase the window in which vaccine could be supplied to the market.

These efforts must not be limited to the coming influenza season but need to be continued for the long term if the Healthy People 2010 goals of 90 percent coverage rates of non-institutionalized adults 65 years of age and older and 60 percent coverage rates of high-risk non-institutionalized adults 18-64 years of age are to be attained.[12] While these goals are ambitious, they are achievable if both the public and private sector join forces in a multi-year effort. The National Influenza Vaccine Summit organized by the American Medical Association in collaboration with the CDC that brings together key stakeholders in the private and public sector is a vehicle that is already working on these goals and Chiron is actively involved in the Summit and believes it can provide the leadership

[11] Source: Morbidity and Mortality Weekly Report Vol. 52 no 41.
[12] The target rate for institutionalized adults aged 18 and older is 90 percent.

required to champion initiatives aimed at raising coverage rates for influenza. The success of such partnerships in raising immunization rates for pediatric vaccines demonstrates how this approach can achieve positive results. It is recognized that there are differences between influenza vaccination and the pediatric immunization situation, where school entry mandates played an important role in raising coverage rates. Nevertheless, it is felt that some of the lessons learned would be applicable.

Immunization of contacts of high-risk individuals represents an additional strategy for protection of persons at high-risk for complications from influenza. Persons who are clinically or sub-clinically infected can transmit influenza virus to persons at high risk for complications from influenza. Decreasing transmission of influenza from caregivers and household contacts to persons at high risk might therefore might cause a reduction in influenza-related deaths and hospitalization among high-risk populations. Health-care workers (HCWs), due to the nature of their occupation, are often in contact with high-risk individuals and therefore the ACIP and other major medical groups and nursing organizations have recommended that HCWs should be vaccinated against influenza. Despite the recommendations coverage rates among HCWs are less than 40%[13]. Chiron believes that significant efforts need to be devoted to increasing immunization coverage rates in this group. First, improving coverage rates will protect health-care workers, their patients, and communities. This will improve prevention, patient safety, and reduce the disease burden. Second, health care workers are an important source of information on immunization to the general population and must lead by example. An unvaccinated healthcare worker is not a credible advocate for immunization and therefore a first step to convincing the general public to get immunized against influenza is ensuring health care workers are vaccinated.

In order to raise coverage rates among health care workers Chiron believes the following is needed:

- HCWs should be provided with easy access to influenza vaccine
- Resources should be committed to institutionalizing immunization of HCWs in their workplace
- Professional health care organizations should develop policies to support HCW immunization and encourage constituents to educate HCWs about the benefits of immunization
- Health-care workers' influenza immunization rates should be regularly measured and reported.

In this context Chiron supports the recommendations made by the National Foundation of Infectious Disease in its call to action *Influenza Immunization Among Healthcareworkers* [14] and encourages professional health care organizations and institutions to follow them.

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[13] Source: Morbidity & Mortality Weekly Report 2003, Vol. 52 RR8
[14] http://www.nfid.org/publications/hcwmonograph.pdf

As Immunization of contacts of high-risk individuals represents an additional strategy for protection of persons at high-risk for complications from influenza, Chiron was pleased to see that the ACIP had added language to its Recommendations on Prevention & Control of Influenza stating that " *ACIP plans to review new vaccination strategies for improving prevention and control of influenza including the possibility of expanding recommendations for use of influenza vaccines* "[15]. At present roughly 60% of the United States population are covered by the recommendations as it is estimated that 185 million individuals fall into the required categories. Therefore moving to a universal recommendation is not that great a leap. The experience of the Canadian province of Ontario in implementing a universal recommendation is encouraging as coverage rates were increased in both the general population and in high-risk groups.

Pandemic Influenza

A universal recommendation for influenza immunization would offer significant benefits for pandemic preparedness, as it would increase demand and therefore the supply of influenza vaccine available in the event of a pandemic. An influenza pandemic occurs when there is a major change (shift) in the influenza virus such that the majority of the world's population has not been previously exposed to the strain and is therefore extremely vulnerable to the virus. Influenza pandemic is a major public health threat with the potential to cause a rapid increase in morbidity and mortality. Three pandemics occurred in the 20th century, the first in 1918. It is estimated that approximately 500,000 deaths due to influenza occurred in the United States between September 1918 and April 1919 and that the pandemic caused 20 million deaths worldwide. The 1918–1919 pandemic was the worst pandemic recorded, and mortality in more recent pandemics has been lower. The Asian influenza pandemic of 1957 is estimated to have caused approximately seventy thousands deaths in the United States while the Hong Kong influenza pandemic of 1968 is estimated to have caused 33,000 deaths.

Immunization of individuals with a pandemic strain specific vaccine is likely to be the most important public health intervention for preventing morbidity and mortality from pandemic influenza. Therefore during the inter-pandemic period it is important to take the required steps to ensure that a pandemic vaccine can be developed as quickly as possible in the event of an influenza pandemic. Chiron welcomes the steps the National Institute of Allergy and Infectious Diseases (NIAID) has taken as part of the NIAID Influenza Pandemic Preparedness Plan to support the manufacture and production of a candidate vaccine against a pandemic strain of avian influenza. Chiron is contributing to this effort through participation in two projects. It is producing pilot lots of investigational H5N1 vaccine at its Liverpool facility using the production process used for its marketed flu vaccine, Fluvirin®. Chiron Vaccines will produce 8,000 doses of the H5N1 vaccine for the NIAID, who will conduct clinical studies exploring the safety profile and immunogenicity of two different doses. It is also producing pilot lots of an investigational vaccine based on an H9N2 at its Siena facility. Different dosages of the vaccine, based on an inactivated strain of the virus developed by the CDC, will be prepared. Some dosages will contain Chiron's MF59 adjuvant—a substance designed to boost the vaccine's protective effect. Chiron will first test the general safety of these

[15] source: Morbidity and Mortality Weekly Report Volume 53

different formulations in laboratory animals and, based on its findings, will then produce 4,000 single-dose syringes of each for clinical evaluation in healthy adults. NIAID will perform a Phase I trial, currently slated for early next year, to test the safety and effectiveness of each formulation in humans. Chiron believes that these sorts of partnerships are crucial to ensure the availability to the public of safe and effective vaccines against avian influenza as soon as possible and that additional investments should be considered once the results of these trials are available.

The draft Pandemic Influenza Preparedness and Response Plan recently published by the National Vaccine Program Office addresses the issue of pandemic vaccine research and development in the inter-pandemic period. Chiron supports the recommendations of the report on the enhancements that can be made to the vaccine development infrastructure during the inter-pandemic period particularly the creation of libraries of reassortant influenza viruses suitable as reference strains for vaccine production, the use of new molecular techniques such as "reverse genetics" to produce high growth reassortant viruses, evaluation and licensure of an influenza vaccine that includes an adjuvant and development of new technologies such as flu cell culture. In addition, Chiron believes that support for the research priorities outlined in the report will encourage investigation into the development of new influenza vaccines that are not based on the current antigens or production techniques. This research may not only lead to a better pandemic vaccine but may also lead to a vaccine that provides better or longer term protection in the inter-pandemic period.

Vaccine Supply in a Pandemic

From the perspective of an influenza vaccine producer, planning for a pandemic represents a significant challenge due to the nature of influenza vaccine production. Essentially, the following factors limit the ability to rapidly expand supply in the face of a pandemic under current circumstances:

- **Production capacity**—Influenza vaccine production capacity is aligned with annual demand for vaccine under normal circumstances, i.e., between pandemics, and therefore little or no surge capacity exists to meet pandemic demand.
- **Inability to stockpile**—Stockpiling of vaccine in preparation for a pandemic is not a viable strategy, as it is not possible to predict the vaccine strain that will cause the pandemic.
- **Supply of primary production material**—Currently, vaccines are produced using eggs, and ensuring an adequate supply of eggs to significantly increase production during a pandemic represents a significant challenge.
- **Specialized production facilities**—Additional quantities of vaccine could not be readily produced in facilities used for other vaccines, as production and purification equipment and facilities are specifically designed for influenza vaccines.

In the event of a pandemic, Chiron will strive to fulfill its responsibility to supply vaccine to the United States and international markets. Chiron has plans to maximize production of influenza vaccine at its Liverpool, Marburg and Siena facilities to help overcome these

challenges in the event of a pandemic. The following steps would be undertaken to increase vaccine production:

- **Year-round production**—Influenza vaccine production would be run continuously over the whole year as opposed to the current seasonal production cycle. However, it should be noted that this assumes that additional egg supply will be available to keep the facilities running year round.
- **Monovalent vaccine**—A monovalent vaccine containing the pandemic strain only would be produced as opposed to the standard trivalent vaccine containing three strains. Manufacturing capacity would therefore be increased by a factor of three, assuming that the vaccine contains the same amount of antigen as the conventional influenza vaccine.[16] Any increase in the antigen content of the pandemic vaccine would result in a proportional reduction in the number of doses that could be produced. At present, the clinical data available to support the definition of the pandemic vaccine is limited.

Chiron estimates that implementing these two steps in the event of a pandemic would more than triple its influenza vaccine manufacturing capacity, of which 50 percent would be produced at its FDA-licensed facility in Liverpool, assuming the pandemic vaccine contains the same amount of antigen as the normal vaccine. By the end of the decade, under its current plan, Chiron anticipates being able to increase its pandemic vaccine production by an additional 50 percent due to expanded production capacity in Liverpool and the availability of a cell-culture facility in Marburg producing its MDCK–based cell-culture vaccine.

It is important to note that the current regulatory approval process would have to be expedited in order for manufacturers to rapidly convert to producing a monovalent pandemic vaccine in a timely fashion. Under the present system, obtaining regulatory approval could be a bottleneck in supplying pandemic vaccine. Chiron believes that discussions and planning should occur now between manufacturers and the FDA in order to determine the regulatory pathway for approval of a vaccine, including any amendments to official release requirements in the event of a pandemic. This would be of significant value to expedite the availability of supply should the pandemic occur.

In the face of a potential influenza pandemic, switching production to a monovalent pandemic vaccine imposes a significant financial risk: If the predicted pandemic failed to materialize, there would be no demand for the monovalent vaccine, and Chiron would be forced to destroy the vaccine. Therefore, Chiron would be unlikely to make the decision to switch production from trivalent vaccine to a monovalent pandemic strain without a guarantee that its production would be purchased whether or not the pandemic materialized. Chiron would be unable to assume this risk without financial guarantees being in place due to the severe consequences of losing an entire year's revenues

[16] It should be noted that studies of experimental vaccines produced in response to the avian influenza A outbreaks in Hong Kong suggest that a greater dosage or an adjuvanted vaccine may be required. Therefore, whether this assumption will turn out to be valid is open to question.

generated from the production of influenza vaccine. Therefore, in order to trigger a switch to pandemic vaccine production as quickly as possible in the event of a potential pandemic, governmental contract authority to purchase pandemic vaccine production by an agreed-upon mechanism of compensation should be in place prior to a pandemic. Such a contractual agreement between vaccine manufacturers and the government implies a limited role for the private sector in the marketing of a vaccine in the event of a pandemic. National governments will procure the vaccine, be responsible for its distribution and determine the priority of immunization. Based on these considerations, Chiron assumes that in the event of a pandemic, the market for influenza vaccine will be almost exclusively a public-sector market, with national governments purchasing vaccine from producers.

Chiron recommends that a mechanism for indemnifying manufacturers, similar to that for smallpox and swine flu, be established in advance of a pandemic situation. The United States Government must indemnify and hold harmless producers of influenza vaccine if they are to manufacture the vaccine in the event of a pandemic. Under section 304 of the Homeland Security Act of 2002, "covered persons," including manufacturers, are deemed to be PHS employees, so that the United States is the exclusively liable party under the FTCA for any injury or death arising out of the administration of a "covered countermeasure" against smallpox during an "effective period" defined by HHS declaration.[17] It is vital that Congress enact a similar provision for manufacturers producing influenza pandemic vaccines.

Despite a potential increase in the supply of vaccine by a factor of greater than three, there will be a global shortage of influenza vaccine in the event of a pandemic. Demand for influenza vaccine would increase dramatically compared to normal circumstances due to the need to immunize most of the global population and a potential increase in the number of doses required per person to provide immune protection from one to two. Current global influenza vaccine production capacity, estimated at roughly 300 million doses in a typical year,[18] will most likely be unable to cope with global demand, and therefore a shortage of vaccine is expected to occur.

Chiron is committed to maintaining supply to the United States in the event of a pandemic. However the current location of Chiron's influenza manufacturing facilities outside of the United States imposes constraints on its ability to ensure this occurs, as it is not clear how global allocation of the vaccine will take place in the event of a pandemic. Where demand outstrips supply, it is possible that national authorities will impose constraints on the allocation of influenza vaccine by manufacturers under their jurisdiction. One of the constraints that may be imposed by national authorities is that producers be required to give priority to meeting national demand before shipping vaccine supply to traditional markets. For example, Chiron could be asked to give precedence to the United Kingdom in allocating vaccine supply from its Liverpool facility, as it is the only domestic source of supply for that country. Furthermore, once the needs of the United Kingdom were met, priority might be given to other European

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[17] *See* 42 U.S.C. § 233(p)(1)-(2), (7).
[18] Chiron internal estimate.

countries before allowing vaccine to be made available to the rest of the world. In addition, manufacturers with facilities located in European Union countries may be required by their national authorities to give precedence to the needs of other EU member countries once domestic needs have been met before vaccine can be exported outside of the EU, particularly for those member states that do no not have domestic production capacity. These variables are real and uncharted. Chiron believes it is important for the United States, United Kingdom and EU authorities to engage in discussions on pandemic influenza vaccine supply in advance of an outbreak in order to clarify supply priorities for its Liverpool facility and would welcome the opportunity to participate in the discussions.

The draft Pandemic Influenza Preparedness and Response Plan recently published by the National Vaccine Program Office also provides encouraging signs for increasing capacity. Chiron fully supports the statement contained in the document that *"Implementing strategies to increase annual vaccine demand and use during the inter-pandemic period will encourage manufacturers to respond with increased supply thus increasing production capacity which will contribute directly to pandemic preparedness"*. Chiron is committed to investing to increase its production capacity if demand for influenza vaccine in interpandemic years continues to increase. However, investment in increasing the supply of vaccine will follow increased demand.

In conclusion, an influenza pandemic will represent a significant challenge to Chiron, as it will need to rapidly expand influenza vaccine at the expense of other products in its portfolio. Recognizing this challenge, Chiron is committed to supporting global pandemic preparedness efforts prior to the inevitable occurrence of a pandemic. Chiron believes that over the past year the United States Government has taken significant steps towards addressing some of the key issues identified below and recommends that the Congress and the Public Health Service focus on the following critical priorities after the November elections.

- Strategic public education programs to increase demand for influenza vaccine during interpandemic years to assure increased supply of influenza vaccines from year to year, thus increasing supply in a pandemic situation.
- Research and development efforts to determine whether or not pandemic vaccine supply can be expanded by adjuvantation of the vaccine.
- Identifying the regulatory pathway for approval of a pandemic vaccine, including any amendments to official release requirements in the event of a pandemic, as well as assurance to manufacturers that there will be flexibility within the regulatory process to rapidly advance clinical trials to coincide with the influenza cycles so that clinical testing will not be delayed.
- Implementing mechanisms to trigger the switch to production of a monovalent pandemic vaccine, whether or not the pandemic materializes, through an agreed process.
- Establishing in advance of a pandemic situation a mechanism to indemnify influenza manufacturers and provide for a compensation program for recipients of the pandemic vaccine should it prove necessary.

In summary, Chiron has invested heavily in ensuring that the United States has a supply of influenza vaccine in inter-pandemic years, which will contribute to protecting the elderly against morbidity and mortality due to the disease. Chiron is committed to providing leadership in the U.S. influenza market. Chiron is shouldering the necessary risks to expand its ability to increase supply and is bringing cutting-edge technologies in influenza cell-culture production to the U.S. market. Fundamental to Chiron's success in realizing its commitments is the ability to work collaboratively with Congress, the Administration and public health officials to reach the immunization rates established in Healthy People 2010 while incentivizing the private sector to transition to new technologies in influenza immunization. These priorities are of critical importance if we are to effectively protect the population as it against influenza as it continues to age and position the United States for preparedness for a global influenza pandemic.

Thank you for the opportunity to present the views of Chiron Corporation. I am happy to answer any questions you may have for me.

The CHAIRMAN. Howard, thank you very much, and again to all of you I appreciate your presence here. I have several questions for each of you. Janet, in regard to the gaps in the draft plan that you have mentioned, which areas do you believe or area is most important to address?

Ms. HEINRICH. There are several, and it really is settling the issues of: is it the private sector or the public sector that will be purchasing the vaccine, who will be distributing it, how, and then the issue of prioritizing the populations that will be at risk knowing that there is going to be a short supply is absolutely critical.

The CHAIRMAN. Yes. Of those areas that you have identified or expressed concern about, which would be the easiest to fix?

Ms. HEINRICH. I think that the discussions have been ongoing about the public-private sector purchase and distribution, and I know from health departments, state and local, there really is an interest in having a Federal Government system in place or that could be used to distribute the scarce vaccine.

It would seem to me that with the growing cooperation between manufacturers and the public sector that that would be the area that probably could be determined.

The CHAIRMAN. Then let me ask this question. Do you believe then that CDC should dictate which population should be prioritized and make decisions for states on how they distribute and administer vaccines?

Ms. HEINRICH. I do not think that approach would be welcomed by the states or the localities. There has to be dialog. There has to be conversation, and what we are hearing, though, is that the states want guidance, and in terms of setting priority populations, there needs to be a discussion among all the stakeholders about which populations would receive the vaccine.

The CHAIRMAN. Well, Carol, with that question, we will turn right to you, and let me ask the same question of you. In your relationship or the relationship of states to CDC and how we make these priorities, what would some of your recommendations be?

Ms. MOEHRLE. The priority I think that I would have personally would be the distribution issue.

The CHAIRMAN. Yes.

Ms. MOEHRLE. There needs to be some bigger oversight of where that vaccine goes first or to make sure that those administering vaccine to the highest risk, wherever that population is, has their vaccine. The distribution seems to be an issue that is of most concern at the local level.

The CHAIRMAN. Yes. It is disturbing to me that large chain store might have it and you do not.

Ms. MOEHRLE. Or physicians do not.

The CHAIRMAN. Or physicians do not.

Ms. MOEHRLE. Or nursing homes do not. Yes, where those high risk are.

The CHAIRMAN. I mean that is obviously tremendously frustrating for the public to call in and say, "I need help or I need to be vaccinated," you say, "I cannot," and Wal-Mart is saying, "I can." That is an interesting juxtapose here.

Do local providers usually order their entire supply from one manufacturer or do they spread the risk and order from more than one; do you know?

Ms. MOEHRLE. From my perspective and what we do at the health districts in Idaho, we usually order from more than one. Because of the variations over the past years, where we get a partial shipment from the manufacturer or our distributor, at different times during the season, if we order from several companies or both companies, we sometimes get a larger shipment right up front, so we do not have to wait till the end to receive those doses. Most of us in Idaho order from several or from both companies.

The CHAIRMAN. Any reaction to what Howard has mentioned today as it relates to supply?

Ms. MOEHRLE. We are hopeful this supply will be there. I also appreciated his comments about getting the message to the media, that everything is safe, they didn't take the chance. They are making sure that things are safe before our public receives that dose.

The CHAIRMAN. That phone call that you got from that one elderly person, bad versus good?

Ms. MOEHRLE. Right. I think there is a negative sentiment out there——

The CHAIRMAN. Yes.

Ms. MOEHRLE [continuing]. In our communities, and then we need to do some real hard media work to make sure that they understand how safe that vaccine truly is.

The CHAIRMAN. Yes, I think that is very important. I think you are to be commended for your partnership efforts to expand your outreach efforts in addition to the program you have mentioned.

Where are the hard-to-reach senior citizens most? In the ruralist of populations?

Ms. MOEHRLE. Well, I am from very rural, as you know. The ones that we see——

The CHAIRMAN. Actually we call that urban in Idaho.

Ms. MOEHRLE. Urban, yeah. [Laughter.]

I think it is frontier in a lot of areas.

The CHAIRMAN. I think you are right.

Ms. MOEHRLE. Some of them it is a transportation issue, which you know in Idaho, they just cannot get to their physician or their clinic in a timely manner. So by having some of our nurses go out to them is very helpful. I think we have definite populations in our cities that do not take advantage of the vaccine either, and it is a personal choice sometimes as well as an option for them not to be able to travel, but we are trying real hard.

This was a pilot in our rural areas, specifically, to see if we could increase the flu availability to those that are in those very, very rural areas.

The CHAIRMAN. How much authority does a local health department have to reallocate vaccine supply when shortages occur?

Ms. MOEHRLE. Authority—partnerships, different. We have lots of partners in our communities and are respected highly with our medical partners, and I think that is why we have seen the willingness for them to actually turn over doses to the public health district to reallocate where they are needed most.

I am sure that partnership is different state to state and jurisdiction to jurisdiction.

The CHAIRMAN. Are you suggesting this is all largely done on a voluntary basis then——

Ms. MOEHRLE. Totally voluntary.

The CHAIRMAN [continuing]. Or collaborative voluntary basis?

Ms. MOEHRLE. Exactly. Totally voluntary, based upon the respect in the partnership.

The CHAIRMAN. It works?

Ms. MOEHRLE. It has worked well in Idaho.

The CHAIRMAN. Well, again, thank you very much for being with us today, greatly appreciated.

Howard, again, thank you for being with us. Will you delay in shipment the Fluvirin; is it?

Mr. PIEN. Fluvirin.

The CHAIRMAN. Fluvirin vaccine composed—let me see. Now I understand what I am trying to say here. Will this delayed shipment compromise the ability of older Americans to obtain the influenza vaccine this year; do you think?

Mr. PIEN. We expect not. As you had heard from a gentleman representing the CDC, there are guidelines and recommendations out of there that says that vaccination, even as late as December, will do good. We expect that in the next few days we can make our distribution plans and shipment plans, in which case the majority of the doses that I spoke of, 46 to 48 million doses, will be shipped in the month of October. Most Americans do get vaccines in the month of October and November.

I should say one more word about supply. This is only our second year as a supplier of flu vaccine to the United States. Nonetheless, last year, our first year, we increased the output by 50 percent. This year if our expectation proves true, as we currently expect that it would turn true, 46 to 48 million doses, that would raise the supply by yet another 20 or so percent.

Therefore, for the total industry, we expect this season we will have about 20 to 25 percent more doses in the United States. So while indeed there are reasons to be concerned about the pandemic situation, as to whether or not enough vaccines will be made, the truth of the matter is that, and a lot of work needs to be done there, as we have already testified, but in the so-called normal flu season, we certainly believe that a commitment of manufacturers to step up to the plate and make more products are clear and present and well demonstrated.

The CHAIRMAN. Has a delay occurred in the delivery of Fluvirin to the U.S. market previously and what guarantees do we have that Chiron will not have a similar situation again next year? I say that because it is obvious that you are a major player in the market.

Mr. PIEN. I have said already in my testimony, we are greatly pained by any disruption and uncertainty that we may have caused. We hope that in due course and in the next few days when we make an announcement, that that issue would no longer be. But let me just say that since a year ago, we began to make the investment to the tune of about $100 million for this year and next to upgrade our manufacturing capacity, to obtain more equipment

and machinery, to train our workforce even better, to increase the state-of-the-art capacities of managing the process of making flu vaccines.

It is our deep and unerring commitment that we are going to do better and be a reliable and consistent supplier.

The CHAIRMAN. Well, Howard, your presence here today probably answers this question because you have heard it said—I have asked the question as a result of what Carol has mentioned—but out in the public, we have heard about people asking for the good vaccine and their lack of confidence in the availability, and you have expressed it very clearly as it relates to the safety of the vaccine.

I think for all to hear, it would not be bad to say it again.

Mr. PIEN. Thank you, Senator. Let me just go back a little bit on what happened in this situation. The flu vaccine, as you heard, is a different product every year.

The CHAIRMAN. That is right.

Mr. PIEN. To reflect the different patterns.

The CHAIRMAN. In saying that, tell us what the shelf life is of a flu vaccine?

Mr. PIEN. Theoretically, it could be longer than one season, but as the virus mutates or drifts every year, the product is actually different every year.

The CHAIRMAN. Obsolete.

Mr. PIEN. Obsolete. Reflecting the fact that the resistant pattern, mutation pattern has changed. Now, it turns out of course that flu vaccine is made up of three strains, so actually it is not one product that is different every year, but three products that are different every year. For that reason, the manufacturing process is complex, and for that reason, there has to be robust consistent routine testing procedures to ensure that the product that is made is indeed safe.

In our situation, we detected some small number of batches of the products that we made appeared to have had contaminated, and the testing procedure and protocol calls for a program that has three components. The first one of which is to retest all of the products that we have made. The second thing is to identify all of the possible hypotheses as to why there might be contamination. The third is to do all of the experiments to rule out all of the alternative explanations such that we lock in on a root cause, as it is called in the trade. Root cause is what we now have come to, and we are doing the documentation literally on thousands of pieces of data and submitting in our final write-up of those testing results to the regulatory authorities, and have the discussion with the regulatory authorities on what it is that we have looked at what we had encountered early on these testing anomalies.

That is why it takes all this time, and that is why I think it is critically important that Americans understand that there is a huge amount of routine testing protocols and procedures and system in place to ensure that there is not going to be any unsafe product that is released.

The CHAIRMAN. I appreciate your walking us through that. I think the average person does not even begin to comprehend the complication and the sophistication of arriving at that, if you will,

new designer vaccine literally every year that fits the circumstance and the mutation of the change of the virus we are dealing with.Thank you.

Your testimony cites the importance of public-private partnerships in addressing the important policy issues surrounding influenza and pandemic planning. Can you provide for the committee some of your thoughts with regard to priorities that should be considered?

Mr. PIEN. We really think that the most important thing is before the pandemic arrives, that we increase the uptake for flu vaccine during the normal season. I think as that happens, the manufacturers are able to make more and more investments and increase their manufacturing capacity. I think that is the first and most important point.

The CHAIRMAN. Capacity in other words?

Mr. PIEN. Capacity to make more products. I think there are several obstacles that are along the way before all of these investments are going to take shape, that is in the overall system. One obstacle is indemnification or coverage from an insurance standpoint. Another one is to define very clearly with the guidance of the Centers for Disease Control and the FDA on how a pandemic vaccine can be made in a short period of time, and once it is made, how the product will be purchased and therefore how it will be distributed.

I think that to wait until the pandemic is upon us, will be too late. The reaction time will be too short. There are new technologies that we have heard descriptions of from NIH and the one that is most promising is called cell culture, which mean that you can make vaccines without a reliance on eggs. Right now it takes 5 months to make vaccines because of the big amount of time it takes to get the eggs and to grow the seeds in the eggs, so that you can harvest the vaccine.

There is the potential that a cell culture vaccine can reduce the reaction time from what is about 5 months now to maybe 2 months, and those kinds of research and development programs need to take place. Chiron is one of the companies that is in this field, and we hope that in a short period of time, we will have things to report on the progress in that area.

The CHAIRMAN. Well, you just mentioned indemnity, liability, compensation programs that are necessary to establish in advance of a pandemic. If these programs are not in place, will Chiron be able to initiate production of the kind that we see necessary for the pandemic flu vaccine?

Mr. PIEN. Senator, the fact is that we are committed in this field. But our commitment right now is to come up with this new product that I have just described, cell culture product that reduces the amount of the manufacturing time to something that is more acceptable. That will cost to something in the range of $100 million of R&D investment.

Beyond that, we have to make a capital investment. We need to make sure that we have the facilities and the machinery and equipment that will make this new generation of cell culture product. That round number is another $100 to $200 million worth of investment.

Now, we are committed to coming up with a new product. If we do not come up with a new product, then all of the questions about incremental investment is theoretical. But certainly, as we get to the point of being able to say with some high degree of certainty that a cell culture product is in our hands, we can actually get registration, and get FDA approval, then it comes a time to make the next chunk of significant commitment, and that is the time we hope that would mature much of this policy discussion and advance many of the policy issues that we have submitted in our testimony. Once again, we think that with political will and with the leadership that certainly this committee represents, what you have just asked me, we would never have to confront.

The CHAIRMAN. Well, I hope that is the case. You heard Carol express the frustration of local health officials that a seemingly random order in which vaccine deliveries occur. Can you shed some light on this for us and how does this distribution process work for you all?

Mr. PIEN. I am not sure that I have a clear answer. Let me give you the background on why. We are still young at being a supplier in the United States. What we do is we work through seven national distributors. We do not ship the products ourselves directly, except in the case of CDC, CDC's safety stock stockpile, as well as CDC's order, which is actually a competitive tender.

So with CDC, we do ship directly, but otherwise, we rely on the distributors. It is the distributors that end up shipping the products to physician's offices, to the public health clinics, or to the retail outlets.

The CHAIRMAN. I see.

Mr. PIEN. Generally, based on our relatively young experience, we believe that we are getting the vaccines to the physicians' offices and I am distraught to hear that we are not getting it to important pockets in different parts of the country. It is possible that there may have to be special consideration as to how we satisfy the needs in areas that are not served well by the distributors. But I would have to submit to you in later testimony as to what our thoughts are. It is outside my range of expertise.

The CHAIRMAN. Well, thank you. Before I close out this panel, are there any additional comments that anyone of you would like to make? Janet?

Ms. HEINRICH. I just wanted to say something more about the distribution——

The CHAIRMAN. Yes.

Ms. HEINRICH [continuing]. Of vaccine going to physicians' offices, clinics, health departments, and healthcare providers. We know that the 65 and over population primarily gets their immunizations through healthcare providers. But we also have heard that because of the distribution through intermediaries, that vaccines do not always go to healthcare providers first.

In fact, it was interesting, in today's Post, in the Health section, there was a little ad about finding a flu shot, and they talk about the Maxim Health System, and how that is where to go, and they are in fact supplying the Coscos and the large stores. So I just want to reemphasize that distribution is currently a concern.

The CHAIRMAN. Carol, anything additional you would to make?

Ms. MOEHRLE. From a public health perspective where we do prevention, flu vaccine is one of the most common-sense things we can do for our citizens is help them realize what a preventive nature that vaccine does in helping us stem outbreaks and death from something that is preventable like the flu.

So, the push to get the vaccine, for people to roll up their sleeve is a great public health message. We are here to protect the public, so anytime that we can get more of that vaccine at the local level where those people are, we need to let them know where those clinics are and who is there to help protect them. Most of the citizens that have a primary care physician, that is where they get their vaccine. For those that cannot access that, we need other clinic options for them.

The CHAIRMAN. Thank you. Howard.

Mr. PIEN. I would just say even on the distribution issue that we have identified and discussed, CDC in its characteristic way of wanting to contribute has been conducting conference calls on a weekly basis with ourselves and our distributors. As you heard in the earlier testimony, I think that while this is true, that there is more to be done. The men and women in public health service really need to be congratulated for the great advance and deep dedication that has already exhibited. This is not an issue that can be addressed overnight.

It requires persistence and resolve and leadership that will ultimately lead to a much more salubrious condition than what we have today.

The CHAIRMAN. Well, I thank you all, both our first and second panelists, for being with us today. We will monitor this closely and hope that not only in shaping public policy, this kind of record helps. We think it does, but also importantly, it again expands the exposure to our citizens of the need to get vaccinated. It is obviously critical, especially in certain vulnerable populations, and this committee tries to be an advocate of a particular one.

We do appreciate it very much. The committee will stand adjourned. Thank you.

[Whereupon, at 11:37 a.m., the committee was adjourned.]

APPENDIX

WRITTEN CONGRESSIONAL TESTIMONY

PROVIDED BY AVENTIS PASTEUR

BEFORE THE SENATE SELECT COMMITTEE ON AGING

STATEMENT ON ANNUAL INFLUENZA VACCINATION AMONG THE ELDERLY

September 28, 2004

Congressional Testimony before the Senate Select Committee on Aging
Statement on Annual Influenza Vaccination among the Elderly
Submitted by Aventis Pasteur

Aventis Pasteur welcomes the opportunity to offer our perspective on important issues related to influenza prevention, including how the nation can increase immunization among groups at increased risk for complications of this serious illness. This is particularly important for seniors who have disproportionate levels of complications, which could lead to hospitalization and death from influenza.

About Influenza

Influenza causes significant levels of global morbidity and mortality. According to the U.S. Centers for Disease Control and Prevention (CDC), in the United States influenza is responsible for an average of 200,000 hospitalizations and approximately 36,000 deaths per year. The National Center for Health Statistics reports that influenza, coupled with pneumonia infection, is the nation's seventh leading killer. Influenza-related deaths can result from exacerbations of cardiopulmonary conditions and other chronic diseases.

Epidemics of influenza typically occur during the winter months. Influenza can bring a variety of symptoms including high fever, chills, muscle and joint pain, and extreme fatigue lasting from a few days to several weeks. It can also result in severe complications. Influenza viruses are spread from person to person primarily through coughing and sneezing. Adults typically are infectious from the day before symptoms begin through approximately five days after illness onset. Approximately 30% to 50% of infected persons may remain asymptomatic, but they can still transmit the virus to others.

Influenza can be prevented through annual immunization. While influenza immunization has long been considered a public health priority and is included in the U.S. Department of Health and Human Services' (HHS) *Healthy People 2010* goals, the nation has a long way to go to achieving target immunization levels.

Influenza and the Elderly

Among the groups considered at greatest risk for developing influenza-related complications are the elderly. Rates of serious illness and death are very high among person 65 years or older, with 90% of influenza-related deaths among the elderly. A 2003 study by the CDC found that the primary reason for the dramatic increase in influenza-related deaths in the U.S. since the 1970s is the nation's growing elderly population.

Prevention of infection and the reduction of influenza transmission in health care settings are best accomplished through widespread immunization. The influenza vaccine can also be effective in preventing secondary complications and reducing the risk for influenza-related hospitalization and death among adults 65 years and older with and without high-risk conditions, such as heart disease and diabetes.

Among elderly persons living outside of nursing homes or similar chronic-care facilities, influenza vaccine is 30-70% effective in preventing hospitalization for pneumonia and influenza. Among those residing in nursing homes, the vaccine is most effective in preventing severe illness, secondary complications and death. Among this population, the vaccine can be 50-60% effective in preventing hospitalization or pneumonia and 80% effective in preventing death. The effectiveness in preventing influenza illness often ranges from 30-40%.

In addition, according to a study in an April 2003 issue of *The New England Journal of Medicine*, influenza immunization can reduce an elderly patient's risk of being hospitalized for heart disease or stroke by 19% and 23% respectively. The study also found that vaccinating the elderly reduces their risk of death from any cause by nearly 50% during the influenza season.

While influenza immunization levels increased from 33% in 1989 to 66% in 1999 among persons 65 and older, the nation must strive for continued steady and incremental increases in immunization rates among this population.

Disparities in Immunization Rates

While adult immunization rates for influenza have improved over the past decade, substantial gaps remain between races and ethnicities at the national level among those aged 65 and older. Rates for

whites and African Americans in this age group also vary by state, with some states, such as Georgia and Florida, having larger disparities than others.

Reducing racial and ethnic health disparities, including disparities in vaccination coverage, is an overarching national goal. Although estimated influenza vaccination coverage for the 1999-2000 season reached the highest levels recorded among older African Americans, Hispanic and white populations, vaccination levels among blacks and Hispanics continue to lag behind those among whites. Estimated influenza vaccination levels for the 2000-2001 season among persons aged 65 years and older were 70% among non-Hispanic whites, 52% among non-Hispanic blacks and 47% among Hispanics.

Poor Immunization Rates among Health Care Workers

One group that needs to significantly increase influenza immunization rates is health care workers. They can spread influenza to high-risk patients, including the elderly, during influenza season, yet only 36% of all health care professionals get immunized each year, according to CDC. Health care workers who may be infected with influenza come into daily contact with elderly and chronically ill patients. Every effort must be taken to ensure that they receive influenza vaccine every year not only to protect themselves and their family, but also to prevent transmitting the virus to patients at high risk for influenza-related complications.

Early in 2004, more than 20 U.S. health care organizations issued a call to action encouraging a comprehensive, concerted effort by health care institutions, employers, insurers and allied professional organizations to improve health care worker influenza vaccination rates both to protect patients and to lessen the burden of influenza on our health care system.

Aventis Pasteur and Influenza Vaccine

Aventis Pasteur is the largest and most experienced manufacturer of influenza vaccine in the United States. Our experts partner with the government and the private sector to meet both routine and emerging pandemic needs for national influenza immunization preparedness. We have a history of proven, effective, licensed manufacturing processes for influenza vaccines and possess the ability and the expertise to continue to produce influenza vaccines annually and respond to influenza vaccine supply emergencies. Most recently on September 21, 2004 HHS awarded a contract to Aventis Pasteur to produce influenza vaccine containing an attenuated version of the H5N1 influenza virus strain. H5N1 is

an avian virus strain that recently emerged in Southeast Asia and other countries and continues to circulate with the potential to become a human pandemic strain.

Additionally, Aventis Pasteur has made considerable investments in the development of cell technologies and new alternative delivery methods for inter-pandemic influenza vaccine.
Our continuing investment has made Aventis Pasteur the highest volume and most consistent manufacturer for the U.S. market today. The company has consistently produced influenza vaccine at the highest efficiencies in industry and has demonstrated its commitment to meet the health needs of the U.S. Our facility in Swiftwater, Pa., has steadily increased production of influenza vaccine and this year will produce more than 52 million doses of influenza vaccine, representing approximately half of the doses of influenza vaccine sold in this country.

Increasing Demand for Influenza Immunization

Increasing interpandemic influenza vaccine demand is essential for improving public health today, enabling predictable and steady vaccine supply, and preparing for pandemic influenza.
In 2003, the late season surge in influenza vaccine demand dramatically reinforced the need to develop a national consensus in the U.S. about how to predictably increase the annual demand for influenza vaccine immunization. Manufacturers will respond to increased stable and predictable demand by producing additional vaccine to fulfill this demand.

The amount of influenza vaccine produced by Aventis Pasteur is determined by the number of doses pre-booked by immunization health care providers during the pre-booking period and an allowance for unexpected demand. Due to the timeframe for producing vaccine, we must decide the total number of influenza vaccine doses to produce for the upcoming influenza season prior to the end of July. Traditionally, the company makes a 20% additional allowance above pre-book orders. In 2003, we increased our previous allowance to 35%, or more than 43 million doses. The surge of demand for influenza vaccine this past flu season is the first time the company ever sold out its supply. In all previous years, we discarded 10% to 15% of our production, which represented millions of doses each year.

If orders for influenza vaccine are pre-booked and ordered early, all stakeholders will benefit. In accordance with the goals set forth in *Healthy People 2010*, the objective is to significantly increase immunization across all high-risk groups, including the elderly.

With respect to planning for the 2004-2005 influenza season, pre-booking orders once again drove vaccine production levels, thus proving that demand drives supply. Health care providers prepared earlier than usual for anticipated demand for the upcoming season resulting in an expected vaccine supply of approximately 100 million doses.

The Government's Role

Federal and state government health planners recognize the value of immunizing senior citizens against influenza and they have taken steps to increase immunization rates.

As HHS Secretary Tommy Thompson has acknowledged, by far the best way to achieve increased annual supply of influenza vaccine is to increase the number of Americans receiving annual influenza immunization from the current levels of 70-80 million people to at least the *Healthy People 2010* goal of 150 million people vaccinated on an annual basis. Such planning also includes working with its Centers for Medicare & Medicaid Services (CMS) to ensure the elderly and those who receive health care through public assistance are adequately protected.

In 2002, HHS announced a new "standing orders" policy encouraging nursing homes, hospitals and home health agencies that serve Medicare and Medicaid beneficiaries to make annual influenza and pneumonia vaccination a routine part of patients' health care. Standing orders help ensure permanent entries are placed in patients' medical charts, directing that the patient be told when it is time to get influenza and pneumococcal vaccines. If the patient chooses immunization, appropriate health care professionals can administer the vaccine, without the need for a physician to write a new order each year. Research sponsored by CMS shows a standing order is an effective approach to increasing immunizations.

At the state level, New Jersey, Pennsylvania and Florida have enacted acute care legislation that requires hospitals to inform patients that vaccination for influenza and pneumococcal disease is available and to provide the opportunity to receive vaccination when they are admitted to a hospital for more than 24 hours for a condition unrelated to influenza or pneumococcal disease.

Last year, Medicare increased reimbursement for the influenza vaccine from $8.02 to $9.95 and nearly doubled average payments for vaccine administration from $3.98 to $7.72 per vaccination. The CMS, CDC, the American Medical Association (AMA) and the National Foundation for Infectious Disease (NFID) worked together to raise awareness of these new reimbursement allowances after learning that most providers were unaware of these increases.

Increased CMS and insurance reimbursement for vaccine administration will be crucial for continued increases in vaccination rates and will help to encourage providers to play a key role in encouraging patients, particularly those at high risk for complications of influenza, to be immunized.

Increasing Influenza Immunization Rates among the Aging

While these are all critical steps in decreasing the number of influenza cases, hospitalizations and deaths, legislation alone is not sufficient to significantly raise immunization rates. Vaccination coverage could also be increased if hospitals and other health care facilities were more proactive in administering vaccine to persons during routine health care visits before the influenza season, making special visits to physicians' offices or clinics unnecessary.

Aventis Pasteur has called on the Federal government and DHHS leadership to engage the provider community to induce greater immunization demand and to assure that Medicare, Medicaid and private health insurance encourage influenza immunization.

Congress should fully support these 2010 goals and the initiatives needed to meet them. While there is no need for legislation to address this issue (since it is not a matter of legal authority, but simply one of implementation), Congress should properly use its oversight responsibilities to ensure these goals are achieved by 2010 or before.

Aventis Pasteur also urges Congress to encourage CMS to continue offering immunization in hospitals, nursing homes, assisted living facilities and other centers for seniors. CMS should annually inform all Medicare and Medicaid providers and other parties about influenza recommendations, coverage and reimbursement and the importance of early pre-ordering.

We encourage CDC to support annual widespread practitioner and public education and awareness campaigns. The agency should add routine publication of adult and pediatric influenza immunization rates by risk group and states to help target and measure specific improvements.

To further increase immunization rates, practitioners, managed care organizations, insurers, health care institutions and community-based immunizers must develop, share and implement best practices to run seasonal surge adult immunization campaigns. This begins with timely pre-ordering and may include flexible scheduling of patients, periodic reminders from physicians and implementation of standing orders to offer immunization to meet patient care quality objectives.

Aventis Pasteur is actively involved in the National Influenza Summit established by the AMA and CDC. Comprised of organizations representing physicians, public health, nurses, pharmacists, industry, managed care and community providers, the Summit's message is consistent with the *Healthy People 2010* goal to increase interpandemic influenza vaccination annually in order to immunize 150 million U.S. citizens by 2010.

We must support public health authorities, the National Influenza Summit, national and local advocacy organizations and coalitions to manage sustained, annual public awareness/education programs that are targeted to the needs and preferences of senior citizens. These programs should convey consistent information, articulate key influenza recommendations for the elderly and communicate information regarding the influenza immunization season.

ACIP Recommendations for Children

Aventis Pasteur believes that expanding demand among the elderly is an essential step to promote public health. Yet, it is also important to note that that the Center for Disease Control's ACIP voted in October 2003 to recommend influenza vaccinations for all children 6-23 months of age. The recommendations are intended to take effect with in the current 2004-2005 season. This is important because it will reduce the high numbers of children hospitalized for influenza-related complications.

In support of the ACIP recommendations for a pediatric immunization, Aventis Pasteur has taken significant steps since 1999 to reduce or eliminate the amount of thimerosal in our vaccines, in response

to public health officials' recommendations and to maintain public confidence. The company currently has a preservative-free formulation of influenza vaccine that contains only trace amounts of thimerosal; this is the third immunization season it has been available for use in young children. For this coming influenza season, we increased production of preservative-free pediatric influenza vaccine more than three-fold to 4.6 million doses. We anticipate having a maximum production capacity of 8 million doses of preservative-free influenza vaccine beginning with the 2005-6 season and for several years thereafter.

Expanding production of preservative-free vaccine beyond the 8 million dose level will require a new facility for filling single-dose syringes or vials, which do not require the addition of preservative as in the case of multi-dose vials. Aventis Pasteur began design of a new Formulation and Filling Facility in 2001 and construction is currently well underway. This $80 million building, which is the largest capital expenditure ever made by the company, is expected to go on-line in 2007 or 2008. Once this new filling capacity is available, an increasing proportion of our existing influenza vaccine capacity is expected to be preservative-free.

It should be noted that for each of the three seasons the preservative-free formulation has been available, customer demand has been less than the amount produced.

Aventis Pasteur is committed to protecting America's public health in the fight against influenza through vaccinations and we appreciated this opportunity to express our views on this important issue.

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