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THE NEXT FLU PANDEMIC: EVALUATING U.S. READINESS

HEARING

BEFORE THE

COMMITTEE ON GOVERNMENT REFORM

HOUSE OF REPRESENTATIVES

ONE HUNDRED NINTH CONGRESS

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THE NEXT FLU PANDEMIC: EVALUATING U.S. READINESS

THURSDAY, JUNE 30, 2005

HOUSE OF REPRESENTATIVES,
COMMITTEE ON GOVERNMENT REFORM,
Washington, DC.

The committee met, pursuant to notice, at 10:05 a.m., in room 2154, Rayburn House Office Building, Hon. Tom Davis (chairman of the committee) presiding.

Present: Representatives Davis, Shays, Burton, Gutknecht, Dent, Waxman, Maloney, Cummings, Kucinich, Clay, Watson, and Ruppersberger.

Staff present: Melissa Wojciak, staff director; David Marin, deputy staff director/communications director; Keith Ausbrook, chief counsel; Robert Borden, counsel/parliamentarian; Rob White, press secretary; Drew Crockett, deputy director of communications; Susie Schulte, professional staff member; Teresa Austin, chief clerk; Sarah D'Orsie, deputy clerk; Kristina Sherry, legislative assistant; Leneal Scott, computer systems manager; Phil Barnett, minority staff director/chief counsel; Karen Lightfoot, minority communications director/senior policy advisor; Naomi Seller, minority counsel; Josh Sharfstein, minority health policy advisor; Earley Green, minority chief clerk; and Jean Gosa, minority assistant clerk.

Chairman TOM DAVIS. Good morning. The committee will come to order.

I want to welcome everybody to today's oversight hearing to evaluate the U.S.' ability to respond to the threat of a global influenza pandemic. This is the committee's fifth hearing over the past 2 years on issues surrounding influenza and our public health system's preparedness levels.

The past few annual influenza seasons, as well as the recent spread of avian flu across Asia, have raised the urgent question of whether the United States is prepared to deal with the threat of a flu pandemic. Today, we will assess our public health system's response capabilities at the Federal, State and local levels and determine what additional measures are needed in order to improve preparations and reduce the risks imposed by an avian flu outbreak.

The experts tell us the next flu pandemic is a matter of when, not if. No one knows exactly when it might strike or whether the next worldwide pandemic will be a version of the avian flu, which you will hear today referred to as H5N1 or "avian influenza A," or a different influenza strain.

What is not up for debate is what the stakes are in dollars, resources and human lives. They are enormous. According to experts, the next pandemic would be worse than the Spanish flu, which is estimated to have caused the deaths of 40 million to 50 million people worldwide in 1918 and 1919. Given the global integration of today's economic markets and the capacity for rapid travel from one corner of the globe to another, a pandemic would move around the world in the same amount of time it takes to fly from New York to Tokyo.

This occurred in the case of the SARS outbreak 2 years ago. In the estimation of several international scientists, including U.S. public health officials, a flu pandemic is the largest public health threat facing the world today. Flu pandemics generally occur three to four times per century when novel flu strains emerge and are readily transmitted from person to person. There is a strong feeling among the public health officials that the next one is imminent.

Today, we will examine what actions and planning procedures have been and still need to be taken at Federal, State and local levels to adequately handle a global communicable disease outbreak. Early detection of new strains and the rapid development of effective vaccines are important keys to protecting the public against the flu and anticipating potential outbreaks.

The World Health Organization, the Center for Disease Control Prevention and other public health organizations have been conducting surveillances in Asia, where H5N1 is now circulating and to date has infected and killed more than 50 people in Vietnam, Cambodia and Thailand. The H5N1 flu strain is extremely virulent and most humans lack immunity.

Why is this surveillance so important? As we have heard in previous testimony before this committee, flu vaccines become obsolete following each season and require constant reformulation. Once the next pandemic flu strain has been identified, a vaccine would take at least 4 months to produce. Furthermore, only a few countries have flu vaccine production facilities, and the United States is home to just one of them. Anti-viral medications, which could help alleviate symptoms of those who contract the pandemic flu virus and help reduce mortality levels are considered a strong first line of defense until a vaccine can be produced and administered.

But the United States has only contracted for or stockpiled in its strategic national stockpile enough courses of the anti-viral Tamiflu to cover 5.3 million people, significantly short of the World Health Organization's guideline of 25 percent of the population. So let's do the math. We are about 62 million under the WHO guidelines, and we can cover 5.3 million today.

These statistics are disconcerting and we will be asking our government witnesses today if we should be doing more to protect Americans against the threat of avian flu. I understand some of our witnesses this morning will express concerns about our preparedness levels and Federal funding for States and localities.

I look forward to constructive dialog regarding those concerns. I know we all share the same goal at the end of the day: a public health system that is adequately prepared and equipped to deal with an outbreak of a deadly and contagious disease. We must not

only be preparing for the likely course of events, but we have to be expecting and be able to adjust to the unexpected.

[The prepared statement of Chairman Tom Davis follows:]

Opening Statement of Chairman Tom Davis
Committee on Government Reform
"The Next Flu Pandemic: Evaluating U.S. Readiness"
June 30, 2005

Good morning. I want to welcome everyone to today's oversight hearing to evaluate the United States' ability to respond to the threat of a global influenza pandemic. This is the Committee's fifth hearing over the past two years on issues surrounding influenza and our public health system's preparedness levels.

The past few annual influenza seasons, as well as recent spread of avian flu across Asia, have raised the urgent question of whether the U.S. is prepared to deal with the threat of a flu pandemic. Today, we will assess our public health system's response capabilities at the federal, state, and local levels, and determine what additional measures are needed in order to improve preparations and reduce the risks posed by an avian flu outbreak.

The experts tell us the next flu pandemic is a matter of when, not if. No one knows exactly when it might strike, or whether the next worldwide pandemic will be a version of the avian flu– which you will hear today referred to as H5N1, or "avian influenza A" - or a different influenza strain.

What is not up for debate is that the stakes – in dollars, resources, and in human lives – are enormous. According to experts, the next pandemic could be worse than the Spanish Flu, which is estimated to have caused the deaths of 40-50 million people worldwide from 1918-1919. Given the global integration of today's economic markets, and the capacity for rapid travel from one corner of the globe to another, a pandemic could move around the world in the same amount of time it takes to fly from New York to Tokyo. This occurred in the case of the SARS outbreak two years ago.

In the estimation of several international scientists, including U.S. public health officials, a flu pandemic is the largest public health threat facing the world today. Flu pandemics generally occur three to four times per century, when novel flu strains emerge and are readily transmitted from person to person. There is a strong feeling among public health officials that the next one is imminent.

Today we will examine what actions and planning procedures have been, and still need to be, taken at federal, state, and local levels to adequately handle a global communicable disease outbreak. Early detection of new strains and the rapid development of effective vaccines are important keys to defending the public against the flu, and anticipating potential outbreaks.

The World Health Organization (WHO), the Centers for Disease Control Prevention (CDC) and other public health organizations have been conducting surveillance in Asia where H5N1 is now circulating, and to date has infected and killed more than 50 people in Vietnam, Cambodia and Thailand. The H5N1 flu strain is extremely virulent, and most humans lack immunity.

Why is this surveillance so important? As we have heard in previous testimony before this Committee, flu vaccines become obsolete following each season and require constant reformulation. Once the next pandemic flu strain has been identified, a vaccine would take at least four months to produce. Furthermore, only a few countries have flu vaccine production facilities, and the U.S. is home to just one of them.

Antiviral medications, which could help alleviate symptoms of those who contract the pandemic flu virus and help reduce mortality levels, are considered a strong first line of defense until a vaccine can be produced and administered. But the United States has only contracted for, or stockpiled (in its "Strategic National Stockpile"), enough courses of the antiviral Tamiflu to cover 5.3 million Americans, significantly short of the WHO's guideline of 25 percent of the population. Let me do the math for you: We're about 62 million people under the WHO guidelines.

These statistics are disconcerting, and we will be asking our government witnesses today if we should be doing more to protect Americans against the threat of avian flu.

I understand some of our witnesses this morning will express concerns about our preparedness levels and federal funding for states and localities. I look forward to a constructive dialogue regarding those concerns. I know we all share the same goal at the end of the day: A public health system that is adequately prepared and equipped to deal with an outbreak of a deadly and contagious disease. And we must not only be preparing for the likely course of events, but we have to be expecting, and be able to adjust to, the unexpected.

We have a great selection of witnesses to provide testimony this morning. Dr. James LeDuc, Dr. Anthony Fauci, and Dr. Bruce Gellin from the Department of Health and Human Services will discuss efforts being taken at the federal level to plan and prepare for a flu pandemic. They will also describe preparedness coordination efforts with state and local authorities.

Joining us on our second panel will be Dr. Marcia Crosse of GAO who will discuss lessons learned from previous annual flu seasons that can be applied to pandemic preparedness. Ms. Mary Selecky, Washington State Secretary of Health, will be testifying today on behalf of the Association of State and Territorial Health Officials to provide an assessment of state and local public health departments' ability to respond adequately to a flu pandemic. Dr. Shelley Hearne, Executive Director of Trust for America's Health, which recently produced a noteworthy report that provided an assessment of improvements to the public health system and remaining vulnerabilities. We also invited the two companies who partnered together to research and develop the antiviral Tamiflu, Gilead Sciences, Inc. and Hoffman-La Roche, Inc. to discuss antiviral production capacities and pandemic planning. Dr. John Milligan, Executive Vice President and CFO of Gilead, and Mr. George Abercrombie, President and CEO of Hoffman La-Roche will be joining us to discuss a recent dispute over the Tamiflu license and what impact, if any, it might have on pandemic preparedness. We welcome all the witnesses and their testimony today.

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Dr. Shelley Hearne, executive director of Trust for America's Health, which recently produced a noteworthy report, will provide an assessment of improvements to the public health system's remaining vulnerabilities. We have also invited the two companies who partnered together to research and develop the anti-viral Tamiflu, Gilead Sciences, Inc. and Hoffman-La Roche, to discuss anti-viral production and capacities and pandemic planning.

Dr. John Milligan, executive vice president and CFO of Gilead and Mr. George Abercrombie, president and CEO of Hoffman-La Roche will be joining us to discuss a recent dispute over the Tamiflu license and what impact, if any, it might have on pandemic preparedness.

We welcome all the witnesses today and their testimony.

I would now recognize the distinguished ranking member, Mr. Waxman, for his opening statement.

Mr. WAXMAN. Thank you, Mr. Chairman.

Today's hearing comes at a time of high alert for the public health system. Eight years ago, a lethal strain of influenza skipped from chickens to humans and led to multiple deaths in Hong Kong. The virus has continued to mutate and has become arguably the most serious imminent threat to human health in the world.

From chickens in Hong Kong, the avian flu virus now infects waterfowl species in 10 Asian countries. It infects ducks, domestic cats and even wild tigers. Increasingly, it has skipped the species barriers into humans. Over the last 18 months, more than 100 people have been diagnosed with avian flu in Vietnam, Thailand and Cambodia. Over half have died.

According to experts in infectious disease, this virus may be only a few mutations away from becoming highly contagious and triggering a global public health crisis. This hearing asks a simple question: Are we ready? Unfortunately, we are going to hear the answer: We are not. Our pandemic flu plan is still in draft form. A vaccine against pandemic flu will take months to produce and the global capacity to make such a vaccine falls far short of what is needed. We have a fraction of the anti-viral medication we will need to respond to a pandemic, and our public health system is underfunded and straining.

Last year's flu vaccine shortage exposed confusion and inefficiency in the delivery of key drugs. We have no stockpile of routinely recommended childhood vaccines. There are major shortages

of qualified personnel around the country. If a global pandemic were to start tomorrow, our country and the world would be in serious danger. According to experts, as many as 500,000 Americans could die.

It is unlikely the pandemic will start tomorrow. We are now in the window between the sounding of the alarm bells and the start of an outbreak, so we need to act quickly. A key priority is to finish the pandemic plan. This plan needs to be specific enough so that the Federal Government, States, localities, businesses and private citizens are ready to step into their roles immediately.

A second priority is to mend the gaps in our public health system. We must ensure that our local and State public health departments have the resources to conduct surveillance, organize a local response, and distribute scarce vaccines and anti-viral medications. It is appalling that the administration is proposing to cut support for these activities by $130 million this next year. We must ensure that key vaccines for children are stockpiled so we are prepared if production lines are needed to make a pandemic flu vaccine. We must invest in public health training and infrastructure.

A third priority is to develop the vaccine to make a vaccine quickly and in large amounts. This is a major scientific challenge that will require significant resources. So far, we have spent $4 billion to prepare for a smallpox attack, which is very unlikely, and an anthrax attack which would likely be contained geographically. We have not yet made this type of investment in effort to counter an imminent and catastrophic strain of influenza.

A fourth priority is to stockpile anti-viral medications. Today, we will hear from two companies responsible for the drug Tamiflu, which is the only therapy that is believed to be effective against avian flu. These companies are fighting about who has the right to make the drug. I expect that they will hear a bipartisan message today not to let their dispute interfere with the drug's supply.

The biggest obstacle we have is complacency. For years, public health experts warned the Department of Health and Human Services that it needed a better plan to address the fragility of our vaccine supply, and for years we have heard reassuring platitudes from officials about how everything possible was being done. Yet when we had an actual flu vaccine shortage last year, we learned the truth. The executive branch was caught flat-footed because warning after warning had been ignored.

We need to have a zero tolerance policy for complacency. We need to demand action, not empty promises. Being prepared for pandemic flu is not a Republican or Democratic issue. We need to join together to direct both more attention and more financial resources to this serious threat.

I thank the witnesses for coming and I look forward to their testimony.

Thank you, Mr. Chairman.

[The prepared statement of Hon. Henry A. Waxman follows:]

Statement of
Rep. Henry A. Waxman, Ranking Minority Member
Committee on Government Reform
Hearing on
The Next Flu Pandemic: Evaluating U.S. Readiness

June 30, 2005

Today's hearing comes at a time of high alert for the public health system. Eight years ago, a lethal strain of influenza skipped from chickens to humans and led to multiple deaths in Hong Kong. The virus has continued to mutate and has become arguably the most serious, imminent threat to human health in the world.

From chickens in Hong Kong, the avian flu virus now infects waterfowl species in ten Asian countries. It infects ducks, domestic cats, and even wild tigers. And, increasingly, it has skipped the species barrier into humans. Over the last 18 months, more than 100 people have been diagnosed with avian flu in Vietnam, Thailand, and Cambodia. Over half have died.

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A vaccine against pandemic flu will take months to produce, and the global capacity to make such a vaccine falls far short of what is needed.

We have a fraction of the antiviral medication we will need to respond to a pandemic.

And our public health system is underfunded and straining.

Last year's flu vaccine shortage exposed confusion and inefficiency in the delivery of key drugs. We have no stockpile of routinely recommended childhood vaccines. There are major shortages of qualified personnel around the country.

If a global pandemic were to start tomorrow, our country and the world would be in serious danger. According to experts, as many as 500,000 Americans could die.

It is unlikely the pandemic will start tomorrow. We are now in the window between the sounding of the alarm bells … and the start of an outbreak. So we need to act quickly.

A key priority is to finish the pandemic plan. This plan needs to be specific enough so that the federal government, states, localities, businesses, and private citizens are ready to step into their roles immediately.

A second priority is to mend the gaps in our public health system. We must ensure that our local and state public health departments have the resources to conduct surveillance, organize a local response, and distribute scarce vaccines and antiviral medications. It is appalling that the Administration is proposing to cut support for these activities by $130 million this year.

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The biggest obstacle we face is complacency. For years, public health experts warned the Department of Health and Human Services that it needed a better plan to address the fragility of our vaccine supply. And for years, we heard reassuring platitudes from officials about how everything possible was being done. Yet when we had an actual flu vaccine shortage last fall, we learned the truth: the executive branch was caught flat-footed because warning after warning had been ignored.

We need to have a zero-tolerance policy for complacency. We need to demand action, not empty promises.

Being prepared for pandemic flu is not a Republican or Democratic issue. We need to join together to direct both more attention and more financial resources to this serious threat.

I thank the witnesses for coming and I look forward to their testimony.

Chairman TOM DAVIS. Thank you very much, Mr. Waxman.

Mr. Shays.

Mr. SHAYS. Thank you, Mr. Chairman. Mr. Chairman, thank you for holding this hearing.

I would just say to our witnesses that we are very grateful for the work that they do. I have had a number of visits to the World Health Organization. I think it is one of the world's treasures. They are unbelievable. I just appreciate as well the work that we do in this country.

I would just end by saying that flu is a tremendous practice for biological terror. If we are ready for the flu, we are practically ready for anything. Mother nature gives us this practice, and we should take advantage of it on that level, but obviously most importantly to save lives.

So it is great that we are doing this hearing, and I thank you.

Chairman TOM DAVIS. Thank you very much.

Any other opening statements? Mr. Gutknecht.

Mr. GUTKNECHT. Just real briefly. Again, thank you, Mr. Chairman, for holding this hearing. I think on behalf of all Americans who are learning more about the potential of this pandemic, we want to make certain that we at the Federal level and NIH and others are doing all we can to not only prevent it, but to come up with potential solutions.

So again thanks for this hearing.

Chairman TOM DAVIS. Thank you very much.

Mr. Cummings.

Mr. CUMMINGS. Thank you very much, Mr. Chairman. I thank you for holding this critically important hearing to evaluate our Nation's preparedness to respond to pandemic influenza.

The Chiron Corp.'s inability to supply the United States with the flu vaccine we anticipated for the 2004–2005 flu season exposed the fragility of our Nation's vaccine supply. This colossal failure to get it right last flu season raised some serious questions about our Nation's preparedness to lessen the impact of a more destructive strain of the flu that could trigger a global pandemic.

Avian flu is considered increasingly likely to cause a pandemic. Experts estimate that a pandemic will result in the deaths of over 500,000 Americans and infect 25 percent of the world's population. The Baltimore Sun on June 12, 2004 reported in an article entitled Fears of Flu Pandemic Spearheading Preparations, "The threat of an avian flu pandemic from Asia could cause 12,000 deaths in the State of Maryland early on, with the possibility of many more later."

The article continues by noting that, "More conservative estimates from the U.S. Centers for Disease Control and Prevention suggest 1,600 to 3,700 Maryland deaths and 16,000 hospitalizations." Mr. Chairman, I ask that this article be included into the record.

[The information referred to follows:]

Fears of flu pandemic spurring preparations

The threat of global influenza prompts research, but critics say the efforts fall short.

By Frank D. Roylance
Sun Staff

June 12, 2005

They gathered around a hotel conference table in Howard County, planning for what might be Maryland's worst public health crisis.

The public health and safety experts spun a shocking scenario arising from the threat of an avian flu pandemic from Asia: 12,000 deaths in the state early on, with the possibility of many more later.

More conservative estimates from the U.S. Centers for Disease Control and Prevention suggest 1,600 to 3,700 Maryland deaths and 16,000 hospitalizations. But public health leaders can't be optimists.

"We have to plan for the worst-case event," said Dr. Jean Taylor, who heads Maryland's pandemic-planning efforts at the state Department of Health and Mental Hygiene.

To safeguard Americans against a pandemic that scientists generally agree is inevitable, federal, state and local officials are developing extensive plans encompassing needs such as hospital and mortuary capacity and production of antiviral medication and vaccines. Local health departments have begun identifying locations such as school gyms and community centers that could accommodate temporary hospitals -- space that might be needed for months.

This month, President Bush signed an executive order authorizing use of quarantines for avian flu cases.

Despite the enormous efforts, critics are warning that the federal government hasn't done enough. Among them are Andrew Pavia, chairman of the Infectious Diseases Society of America's task force on pandemic influenza. He told Congress late last month that "the United States is woefully unprepared for a pandemic that might occur in the next few years."

Essential tools

Much of the concern focuses on the nation's capacity to provide antiviral medications and vaccines.

Antiviral drugs like Tamiflu are essential tools in slowing the spread of disease until a vaccine can be developed to immunize people -- a process that can take six to eight months from the time a killer virus is identified. The United States has enough Tamiflu on hand to care for 2.3 million people, significantly less than some other nations.

But federal authorities said substantial progress is being made:

• The Centers for Disease Control and Prevention have paid $13.9 million for the manufacture and stockpiling of 2 million doses of an experimental vaccine for the H5N1 virus, which has killed millions of chickens and a small number of people in Asia. The vaccine is being tested at the University of Maryland School of Medicine in Baltimore and two other sites. It is intended for research, shelf-life studies and, if approved, possibly for limited human innoculations.

• To beef up the capacity of the only flu vaccine plant left in the United States, authorities invested $41 million last fall to expand and maintain the chicken flocks used by the company Sanofi Pasteur in Swiftwater, Pa. By September, that will allow year-round production of the millions of fertile eggs vital to vaccine production.

• Sanofi Pasteur has also won a $97 million contract to develop a technology for vaccine production in a line of human cells, which could reduce by months the time needed to produce a new vaccine.

• A Swiss maker of antiviral medication has committed to producing it in a new U.S. plant next year.

This summer, the National Vaccine Program Office will finalize a Pandemic Influenza Preparedness and Response Plan. State health departments are expected to have their plans ready by September.

But there's only so much the government can do to prepare.

Despite years of worry about an avian flu outbreak in Asia, virologists don't know for sure which virus they would face in a pandemic, where it would evolve, how deadly it will be or how easily it would be passed from person to person.

Pharmaceutical manufacturers can't begin making vaccines until that new virus emerges. Even then, they'll need months, while the disease is spreading, to grow the vaccine proteins in fertilized chicken eggs.

Also, public health authorities, elected officials, hospital managers and health care providers can't be sure that what they'll face will amount to a very bad flu season -- or a public health calamity that exhausts medical supplies, overwhelms mortuaries and brings the economy to a crawl.

But scientists and public health officials are in substantial agreement on this much: Sooner or later, the world will face a severe influenza pandemic, borne by a newly evolved virus against which humanity has little or no natural immunity.

All that's needed to touch it off, scientists said, is a chance exchange of viral DNA inside a single pig or human victim. That could produce a virus with the virulence of H5N1 and the easy communicability of an ordinary flu bug.

If it ever happens, said Dr. John Bartlett, chief of infectious diseases at the Johns Hopkins School of Medicine, "it's going to be awful."

Bartlett said the United States needs to get ready now even if the H5N1 avian flu proves to be a dud. Influenza pandemics have occurred with regularity, and new ones will arise as new viruses evolve.

The "Spanish flu" pandemic in 1918-1919 caused more than 500,000 deaths in the United States and more than 20 million worldwide. The "Asian flu" of 1957 killed 70,000 Americans, and the "Hong Kong" flu in 1968 left 34,000 dead.

Conservative CDC estimates of the toll from a future pandemic in the United States predict up to 207,000 deaths and 734,000 hospitalizations. A virus as nasty as the 1918 flu bug would be expected to kill as many as 1.7 million Americans.

About 100 humans are known to have contracted the H5N1 virus from animals since December 2003, with 54 deaths. Thai authorities reported one "probable" case of human-to-human transmission within a family last year.

The Asian outbreak has focused the attention of public health officials worldwide on finding an effective vaccine.

The University of Maryland and two other universities are testing 8,000 doses of H5N1 vaccine on 450 volunteers to see if it is safe and effective. The vaccine was produced by Sanofi Pasteur under a contract awarded by the National Institutes of Health in March 2004.

Even if it proves effective, experts said there's no guarantee the vaccine will work should a pandemic occur. All influenza viruses are constantly mutating, a process known as "antigenic drift."

"Even one or two changes, if they occur in the right spot, can affect whether the virus would be recognized by the immune system," said John Treanor, a professor of medicine at the University of Rochester and the principal investigator for the NIH trials.

An old technology

Vaccine production still relies on a 30-year-old technology based on millions of fertile chicken eggs.

Sanofi Pasteur maintains flocks of millions of chickens. They produce eggs nine to 10 months a year -- all that's needed to make the vaccines to tackle the routine flu viruses we face every winter.

But that would not be enough to take on an influenza pandemic. The new five-year, $41 million federal contract will help Sanofi expand and maintain its flocks to produce eggs year-round.

The government is investing millions in Sanofi because it is the only remaining manufacturer of influenza vaccines in the United States. Low and inconsistent demand for the annual flu vaccines drove everyone else in the United States out of the business.

FluMist, a flu vaccine that is inhaled, is made in bulk in Britain and finished in the United States. But it is based on a live, weakened virus that might not be safe for patients with weak immune systems.

And in a global pandemic, officials said, the United States would probably not be able to turn to other countries for vaccine supplies. They will be facing their own public health crises.

Several European countries, as well as Japan, Australia, Taiwan, Korea and Brazil, are also developing H5N1 vaccines or building manufacturing capacity.

"The biggest concern I have globally is Africa," said James T. Matthews, director of external research and development at Sanofi. There is no vaccine in development on that continent, and "they are very vulnerable."

Expanding capacity

U.S. health authorities are planning campaigns to encourage more Americans to get annual flu shots, hoping that will increase demand, attract more drug manufacturers and expand the nation's domestic vaccine capacity.

In a pandemic outbreak -- an epidemic over a wide geographic area -- vaccines would arrive late and slowly, officials said. Vaccination priority would go to critical services personnel and to the most vulnerable populations. As more supplies arrived, distribution would broaden to the wider population.

Scientists are also working to determine whether and how a flu vaccine could be formulated or administered differently -- perhaps under the skin rather than into the muscle -- to stretch limited supplies.

Meanwhile, Sanofi is trying to develop a new technology for vaccines that would grow in

human cell lines instead of chicken eggs. The hope is that cell cultures would produce vaccine in as little as a month after a novel influenza vaccine is isolated.

For now, the world is stuck with egg technology, and with the fact that, for months at the start of a pandemic, most of the population will not have been vaccinated.

"If we assume that people will need two doses to be protected," said Dr. Benjamin Schwartz, senior science adviser to the National Vaccine Program Office, "a substantial proportion of the population would not have access to vaccine during that first year" of a pandemic that is likely to last two.

During that period, the United States would have to rely largely on antiviral medicines and infection control to stem or slow the tide of illness.

Stopping it in Asia, or wherever it emerges, would be the first goal. If that fails, antivirals and infection control would be used at home to protect as many vulnerable people as possible until vaccines arrive.

Antiviral medicines can be used to prevent infection. They are also valuable as therapy. Taken within 48 hours of the first symptoms of flu, they can limit the severity and duration of the illness. That helps to slow the spread of an epidemic.

There are two types of antiviral drugs. But the H5N1 virus has developed a resistance to one of them, called adamantines.

That leaves the neuraminidase inhibitors such as Tamiflu, made by the Swiss firm Roche. But there are problems there, too, health officials said: Tamiflu is made in Switzerland, it takes almost a year to produce, and supplies might be restricted in a global pandemic.

Britain and France have set about buying enough antiviral medicine to treat 25 percent and 21 percent of their populations, respectively.

The U.S. government has set no such target. But it has gotten Roche to commit to building a production plant in the United States. "They're anticipating that next year they would begin making the drug here," Schwartz said.

Other remedies

Public health officials said they won't be able to rely on drug remedies alone. In their pandemic plans, experts are looking closely at how best to control the spread of infection in the face of shortages of antivirals and vaccines.

Drawing on bioterrorism and disaster plans, and on their experience with severe acute respiratory syndrome (SARS) and similar recent disease scares, federal and state agencies have begun to work out their pandemic plans.

They include procedures for screening airline passengers arriving from places with pandemic flu outbreaks, educating health professionals to be alert for signs of flu and to ask patients about their travels.

Plans are in the works for isolating sick people and placing people exposed to the virus in quarantine -- at home or in public facilities.

In August, Maryland health officials will conduct a "table top" simulation with state and local school officials to figure out when and how to close schools -- a decision that would have enormous impact on the economy as working parents are forced to stay home with their kids.

Hospitals, too, are hammering out plans for coping with high absenteeism and shortages of empty beds, medical supplies and equipment. Of particular concern are mechanical ventilators, vital for keeping alive flu victims with secondary lung infections.

The list of potential disruptions seems endless -- absenteeism among prison guards and ambulance crews; shortages of blood donors and refrigerated storage as mortuaries are overwhelmed by the dead; a scarcity of volunteers needed to deliver meals and medicines to people isolated at home.

Dr. Peter L. Beilenson, who announced last week his resignation as Baltimore's health commissioner, said the city is better prepared to respond to a bioterrorism attack than a flu pandemic. There are stockpiles of medicines for anthrax and smallpox, he said, but Baltimore lacks the weapons for flu.

"There just aren't the vaccines and pharmaceuticals that we probably need," said Beilenson.

Disturbing prospect

While many public officials have been working on the issue for years, some got their wake-up to these kinds of issues at last year's exercise in Howard County.

"For the few participants who, for the very first time, heard about pandemic flu and what it's implications were, it was stunning," said Jean Taylor, at the state health department.

Seated at the table were representatives from the governor's office, state and local agencies for public health, transportation, public safety and emergency management, as well as leaders representing hospitals, nurses, morticians and academia.

It wasn't just the deaths in the scenario that disturbed them. Medical supplies were in short supply. Absenteeism was soaring. Police, firefighters, medical workers and air traffic controllers were among the thousands of sick, dead or terrified. Hospitals and mortuaries were overwhelmed.

The first small batches of vaccine were arriving, but they were reserved for health care and public safety workers. Crowds gathered, demanding vaccination, and small riots were breaking out.

Planning for such events is valuable even if the H5N1 avian flu bug never mutates into a pandemic virus.

"It's not a question of if, it's when," Bartlett said. "If we know how to respond to avian influenza in terms of building a vaccine and being able to have antiviral agents fast and have all the machinery in place, we'll be ready."

Sun staff writers Jonathan Bor and Michael Stroh contributed to this article.

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Mr. CUMMINGS. One need not be an expert to comprehend the magnitude of this loss of life and the disastrous impact a flu pandemic would cause to our economy and to our society. With this in mind, we must agree to move forward in the best interests of the Nation and achieve our ultimate objective of ensuring that our Nation is capable of effectively and efficiently addressing a flu pandemic. This begins with having a plan, one that covers intergovernmental coordination, the use of the strategic national stockpile, and a process for distributing anti-virals and vaccines.

While the administration took a step in the right direction when it released the draft pandemic flu plan, this plan is unfortunately silent on critical details and is not yet finalized. How the vaccines will be distributed, purchased, prioritized, and what information will be conveyed to the public remain unresolved.

In light of the fact that State and local health departments will function on the frontlines of a flu pandemic, I am deeply troubled that the administration proposed undermining State and local preparedness by cutting $130 million in Federal support of those efforts in fiscal year 2006, with the World Health Organization stating: "Everything suggests that the situation we are in now, there is a greater risk for a pandemic than for many decades." We should increase Federal funding of our public health infrastructure instead of attempting to restore fiscal sanity to the detriment of public health and safety.

It is also critically important to our Nation's readiness that we have adequate supplies of vaccines and anti-virals. While vaccines are considered effective, they are difficult and slow to produce. Regrettably, apparent global capacity to make a flu vaccine will potentially leave billions of people in need during a pandemic.

Equally disturbing is the fact that the United States is particularly vulnerable to a shortage due to limited vaccine manufacturing facilities in the United States. While the Federal Government works to improve our Nation's access to a safe, affordable and effective flu vaccine, it seems prudent that we also obtain anti-viral drugs deemed effective against pandemic flu. It should be noted while the World Health Organization recommends that countries purchase enough of an anti-viral drug called Tamiflu to treat 25 percent of their population, the United States only has enough of this drug to treat 2 percent of the population.

With last year's flu season fresh in mind, we must ensure that no Americans needlessly suffer or die due to poor preparedness. Our Nation must be ready to safeguard our citizens by providing them with either the proper treatment or means to prevent infection in the event of an outbreak. Any less would be a gross abdication of our responsibility to protect citizens from threats both seen and unseen.

I yield the balance of my time and I thank you.

[The prepared statement of Hon. Elijah E. Cummings follows:]

Opening Statement

Representative Elijah E. Cummings, D-Maryland

Full Committee Hearing: "The Next Flu Pandemic: Evaluating U.S. Readiness."

Committee on Government Reform
U.S. House of Representatives
109th Congress

June 30, 2005

Mr. Chairman,

Thank you for holding this critically important hearing to evaluate our nation's preparedness to respond to pandemic influenza.

The Chiron Corporation's inability to supply the United States with the flu vaccine we anticipated for the 2004-2005 flu season exposed the fragility of our nation's vaccine supply. This colossal failure to get it "right" last flu season raised some serious questions about our nation's preparedness to lessen the impact of a more destructive strain of the flu that could trigger a global pandemic.

The Avian flu is considered increasingly likely to cause a pandemic. Experts estimate that a pandemic would result in the deaths of over *500,000* Americans and infect 25% of the world's population. The *Baltimore Sun* on June 12, 2005 reported in an

article entitled, *Fears of Flu Pandemic Spurring Preparations*, that "the threat of an avian flu pandemic from Asia…[could cause] 12,000 deaths in the state [of Maryland] early on, with the possibility of many more later." The article continues by noting that "[m]ore conservative estimates from the U.S. Centers for Disease Control and Prevention suggest 1,600 to 3,700 Maryland deaths and 16,000 hospitalizations."

Mr. Chairman, I ask that this article be included into the record.

One need not be an expert to comprehend the magnitude of this loss of life and the disastrous impact a flu pandemic would cause to our economy and society. With this in mind we must agree to move forward in the best interest of the nation and achieve our ultimate objective of ensuring that our nation is capable of effectively and efficiently addressing a flu pandemic.

This begins with having a plan, one that covers intergovernmental coordination, the use of the strategic national stockpile, and a process for distributing antivirals and vaccines. While the Administration took a step in the right direction when it released a draft pandemic flu plan, this plan is unfortunately silent

on critical details and is not yet finalized. How the vaccines will be distributed, purchased, and prioritized, and what information will be conveyed to the public remain unresolved.

In light of the fact that state and local health departments will function on the front lines of a flu pandemic, I am deeply troubled that the Administration proposed undermining state and local preparedness by cutting $130 million in federal support of those efforts in FY 2006.

With the World Health Organization stating, "Everything suggests, that the situation we are in now, there is a greater risk for a pandemic than for many decades" we should be *increasing* federal funding of our public health infrastructure instead of attempting to restore fiscal sanity to the detriment of public health and safety.

It is also critically important to our nation's readiness that we have adequate supplies of vaccines and antivirals. While vaccines are considered effective, they are difficult and slow to produce. Regrettably, current global capacity to make a flu vaccine would potentially leave billions of people in need during a pandemic. Equally disturbing is the fact that the United States is particularity

vulnerable to a shortage due to limited vaccine manufacturing facilities in the United States.

While the federal government works to improve our nation's access to a safe, affordable, and effective flu vaccine, it seems prudent that we also obtain antiviral drugs deemed effective against pandemic flu. It should be noted, while the World Health Organization recommends that countries purchase enough of an antiviral drug called Tamiflu to treat 25% of their population, the U.S. only has enough of this drug to treat 2% of the population.

With last year's flu season fresh in my mind, we must ensure that no Americans needlessly suffer or die due to poor preparedness. Our nation must be ready to safeguard our citizens by providing them with either the proper treatment or a means to prevent infection in the event of an outbreak. Any less would be a gross abdication of our responsibility to protect citizens from threats both seen and unseen.

I yield the balance of my time and look forward to the testimony of today's witnesses.

Chairman TOM DAVIS. Thank you very much.

Members will have 7 days to submit opening statements for the record. We will now recognize our first panel: Dr. James LeDuc, the Director, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases at the Center for Disease Control and Prevention; Dr. Anthony Fauci, Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health; and Dr. Bruce Gellin, the Director of the National Vaccine Planning Office, Department of Health and Human Services.

As you know, it is the policy of this committee, we swear all witnesses in, so if you would rise and raise your right hands.

[Witnesses sworn.]

Chairman TOM DAVIS. Thank you. Be seated.

Dr. LeDuc, we will start with you and we will move straight down. Thank you very much.

STATEMENTS OF DR. JAMES W. LEDUC, DIRECTOR, DIVISION OF VIRAL AND RICKETTSIAL DISEASES, NATIONAL CENTER FOR INFECTIOUS DISEASES, CENTERS FOR DISEASE CONTROL AND PREVENTION; DR. ANTHONY FAUCI, DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, NATIONAL INSTITUTES OF HEALTH; DR. BRUCE GELLIN, THE DIRECTOR OF THE NATIONAL VACCINE PLANNING OFFICE, DEPARTMENT OF HEALTH AND HUMAN SERVICES

STATEMENT OF DR. JAMES W. LEDUC

Dr. LEDUC. Thank you very much, Mr. Chairman and members of the committee.

I would like to share with you some of the advances that we have made on global surveillance. I will leave comments to the issues surrounding anti-viral drug development and vaccine development to my colleagues Dr. Fauci and Dr. Gellin.

Let me begin with a brief summary of the current situation in Asia. As of yesterday, June 28th, the World Health Organization had reported 108 cases of avian influenza in humans since January 28, 2004, with a case fatality rate of about 50 percent. The World Organization for Animal Health, the OIE, had confirmed H5N1 influenza infections in animals in nine Asian countries during 2004 and 2005, with especially severe outbreaks in Vietnam and Thailand. Although the situation is very serious, there remains no evidence for sustained human-to-human transmission.

We continue to work very closely with the World Health Organization to monitor the situation and indeed the Chief of our influenza branch, Dr. Nancy Cox, is en route back from Vietnam even as we speak, having just completed a mission to Hanoi as part of a WHO team to investigate a cluster of human cases of influenza.

CDC is working closely with health officials in the region to strengthen influenza surveillance capacity. In the last fiscal year, the department provided $5.5 million to WHO and countries of the region to establish or improve their national influenza centers and to strengthen the WHO global network of collaborating laboratories. The goal of these investments is to ensure the earliest possible recognition of strains with pandemic potential to make certain

that the viruses are isolated and made available to the global community for vaccine development, and to assist countries in local control of efforts to prevent widespread transmission.

As part of these efforts, CDC staff are being assigned to the WHO office in Geneva and the regional office in Manila and in the country office in Vietnam. These investments are being leveraged through collaborations with the U.S. Navy laboratories in Indonesia and in Cairo, Egypt and with the CDC International Emerging Infections Program in Bangkok, Thailand. The fiscal year 2005 funding for this effort is $7.2 million. Recently, Congress passed and the President signed a fiscal year 2005 emergency supplemental appropriation which included $25 million in assistance to prevent and control the spread of avian influenza in Southeast Asia. These funds will further support development of improved disease surveillance, training of laboratory and medical staff, preparedness activities, and enhanced communication capabilities.

Here in the United States, we are training laboratory staff in all 50 States to ensure their ability to diagnose avian influenza should it arise. We are expanding our network of sentinel physicians to more accurately monitor the spread of influenza during the flu seasons. CDC has also taken the lead in revising the department's pandemic preparedness plan. The revision, which is scheduled for release later this summer, will be significantly expanded and will provide comprehensive guidance to our partners in State and local health departments. The plan is being developed in cooperation with the Advisory Committee on Immunization Practices and the National Vaccine Advisory Committee, and will offer guidance on prioritization for use of both anti-viral drugs and vaccines.

Finally, CDC is leveraging investments already made in bioterrorism preparedness to ensure that these resources that are already part of the strategic national stockpile are included in our pandemic planning. Mass casualty and surge capacity planning for hospitals is also underway in conjunction with HRSA.

Health and Human Services Secretary Mike Leavitt has made influenza pandemic planning and preparedness a top priority and has chartered the Influenza Preparedness Task Force to prepare the United States for this potential threat to the health of our Nation. As a member of this task force, CDC is proud to undertake these activities with our partners both domestically and globally.

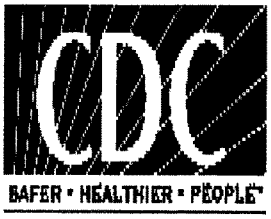
Thank you for the opportunity to share this information with you. I would be happy to answer any questions.

[The prepared statement of Dr. LeDuc follows:]

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

The Next Flu Pandemic: Evaluating U.S. Preparedness

Statement of
James W. LeDuc, Ph.D.
Director,
Division of Viral and Rickettsial Diseases
National Center for Infectious Diseases
Centers for Disease Control and Prevention
U.S. Department of Health and Human Services



For Release on Delivery
Expected at 10:00 a.m.
Thursday, June 30, 2005

Mr. Chairman and members of the Subcommittee, I am pleased to be here today to describe planning and preparedness for an influenza pandemic, including the potential threat posed by the H5N1 avian influenza virus currently circulating in Asia. Department of Health and Human Services (DHHS) Secretary Mike Leavitt has made influenza pandemic planning and preparedness a top priority. Agencies within DHHS are working together formally through the Influenza Preparedness Task Force that Secretary Leavitt has chartered to prepare the United States for this potential threat to the health of our nation.

I will discuss steps the Centers for Disease Control and Prevention (CDC) is taking as a member of this Task Force and with many other partners both domestically and globally. The strength and flexibility of CDC and other components of the public health system are vital assets as the U.S. sharpens its readiness for an influenza pandemic. Although we have made significant progress, more work is needed, particularly in the areas of surveillance capacity and response, and in the development of potential vaccines. Increased public awareness and understanding about infection control, community containment and travel, and other actions also are important in preparation for an influenza pandemic.

In discussing pandemic influenza, I want to emphasize that the issues of pandemic influenza and inter-pandemic influenza (so-called "annual influenza") are inextricably linked. The same laboratories, the same health care providers,

the same surveillance systems, and the same health department plans and personnel will guide both responses. Making sure that these people and organizations can address inter-pandemic influenza is our best overall hope for making sure the U.S. is prepared for an influenza pandemic.

Pandemics in Perspective

Inter-pandemic influenza causes an average of 36,000 deaths each year in the U.S., mostly among the elderly and nearly 200,000 hospitalizations. In contrast, the severity and impact of the next pandemic, whether from H5N1 or another influenza virus, cannot be predicted. However, modeling studies suggest that, in the absence of any control measures, a "medium-level" pandemic in the U.S. could result in 89,000 to 207,000 deaths, between 314,000 and 734,000 hospitalizations, 18 to 42 million outpatient visits, and another 20 to 47 million people being sick if 15 percent to 35 percent of the U.S. population develops influenza in a pandemic. The associated economic impact in our country alone could range between $71.3 and $166.5 billion. A more severe pandemic, as happened in 1918, could lead to much greater damage.

There are several important points about influenza and pandemic influenza.

- A pandemic could occur anytime during the year and could last much longer than inter-pandemic influenza, with waves of infection during the pandemic period.

- At some point in a pandemic, the capacity to intervene and prevent or control transmission of the virus can become extremely difficult because the size of the population that is infected becomes too large.
- Right now, the H5N1 avian influenza strain circulating in Asia among birds is considered the leading candidate to cause the next pandemic. However, it is possible for another influenza virus, and not H5N1, to cause the next pandemic. While we believe some viruses are more likely than others to cause a pandemic, we cannot predict with certainty the risks from specific viruses.
- We often look to history to try and understand how a modern pandemic might affect us and how we might intervene most effectively. However, there have been many changes since the last pandemic in 1968, including changes in population and social structures, medical and technological advances, and the increase in international travel. Some of these changes have increased our ability to handle pandemics, but other changes have made us more vulnerable.
- Because pandemic influenza viruses will emerge in part or wholly from among animal influenza viruses, such as birds, it is critical for human and animal health authorities to coordinate activities such as surveillance and to share relevant information as quickly as possible.

The Current Avian H5N1 Influenza Situation in Asia

For an influenza virus to cause a pandemic, it must (1) be a virus to which there is little or no pre-existing immunity in the human population; (2) be able to cause illness in humans; and (3) have the ability for *sustained* transmission from person to person. So far, the H5N1 virus circulating in Asia meets the first two criteria but has not yet shown the capability for sustained transmission from person to person.

Although the present avian influenza H5N1 strain in Asia does not yet have the capability of sustained person-to-person transmission, at least 100 persons have been infected, largely by having some form of contact with infected poultry, primarily chickens. In addition, a limited number of persons have been infected by very close contact with another infected person, but this type of transmission has not led to sustained transmission or large outbreaks. As of June 17, 2005 the World Health Organization (WHO) had confirmed 107 cases of H5N1 influenza in humans since January 28, 2004, with a case fatality rate of 51 percent. The World Organization for Animal Health (OIE) confirmed, as of June 8, 2005, that H5N1 had been found in animals from nine Asian countries in 2004 and 2005, with especially large outbreaks among animals in Vietnam and Thailand. Millions of domestic birds have been culled in attempts to stop the spread of the virus among animal populations. In addition to poultry, infections among migratory birds may have also been found since 2002.

At this point, the H5N1 strain now appears to be endemic in poultry and other birds in a number of Asian countries. This situation poses a threat to humans because H5N1 from such sources can continue to infect people and because persistence of H5N1 in these populations provides the virus with chances to mutate or reassort its genes with genes from other viral strains and create H5N1 viruses that can transmit easily among people. Recent studies also have found that domesticated ducks can appear healthy but carry and shed the H5N1 strain, allowing the virus to spread invisibly to other species. H5N1 also has been shown to naturally infect mammals, which is a particular concern because this increases the potential for H5N1 viruses to reassort with other influenza strains that already have the ability to spread among humans and other mammals. Studies have documented H5N1 infections of pigs, tigers, and leopards in Asia.

To monitor H5N1 viruses for changes indicating an elevated threat for people, we must continue to strengthen and build effective in-country surveillance, which includes enhancing the training of laboratorians, epidemiologists, veterinarians, and other professionals, and promoting the comprehensive reporting that is essential to monitor H5N1 and other strains of highly pathogenic avian influenza.

Responding to a Pandemic

Although the current situation is very serious, it remains relatively localized to Asia. However this situation could evolve into a pandemic, in which case the entire world's population would be at risk for developing pandemic disease. An

effective response to an influenza pandemic requires highly collaborative planning, implementation, and flexibility in resolving issues at many levels. DHHS is leading the coordination of preparedness efforts through its *Pandemic Influenza Response and Preparedness Plan*, which was released in draft form in August 2004 for public comment and is under revision. In addition, states are either developing pandemic influenza plans or revising existing plans to reflect new information and data. Key elements of these plans include the use of surveillance, infection control, antiviral medications, community containment measures, vaccination procedures, communications, and an ability to sustain essential services in times of widespread illness. To support the federal and state planning efforts, CDC is developing detailed guidance and materials for states and localities, and this guidance will be incorporated into the revised DHHS plan. CDC also is taking a lead role in working with the Advisory Committee on Immunization Practices and the National Vaccine Advisory Committee to recommend prioritized target groups for use of antiviral medications and vaccines during a pandemic when supplies are limited.

In the earliest pandemic stages, isolation precautions for persons who are ill and quarantine for persons exposed probably will be needed to try and limit the spread of pandemic influenza and to obtain as much time as possible for producing supplies of a pandemic vaccine. These control measures will require interventions such as the evaluation of ill travelers. Certain steps have been taken or will be taken to facilitate such efforts. On April 1, 2005, the President

amended Executive Order 13295, adding influenza caused by novel or reemergent influenza viruses that are causing, or have the potential to cause, a pandemic to the list of quarantinable diseases. CDC will implement travel notices to minimize the potential for infection to rapidly spread. Recently, CDC expanded the number and capacity of its quarantine stations at major ports of entry into the U.S. As with any quarantine, such activities need to be undertaken judiciously to minimize adverse effects on civil liberties.

Vaccination is the best overall, long-term strategy to reduce disease from inter-pandemic influenza outbreaks and pandemics. Antiviral medications, which can be used to prevent influenza and in some instances to treat influenza, provide another line of defense. These types of measures, together with those such as isolation of ill persons and quarantine of healthy exposed persons, help form a comprehensive preparedness approach both to address inter-pandemic influenza and to lay the foundation for responding to pandemic influenza.

Surveillance

Surveillance is critical for detecting and monitoring all infectious disease threats. Because early detection means having more time to respond, it is critical for the U.S. to work with domestic and global partners to expand and strengthen the scope of early-warning surveillance activities used to detect the next pandemic. We do not know how long it will take for pandemic disease in another country to spread to the U.S., but it could be a matter of days to months. And yet, months

of time, at best, will be needed to develop, produce, test, and administer vaccine to the entire U.S. population. Vaccine will be in short supply at the start of the pandemic and under the most favorable conditions, many will have become ill or died by the time the first dose of vaccine would be available to be given to the first person in this country. Global surveillance will also be used to monitor ongoing changes in a pandemic virus and thus allow us to know when the vaccine should be updated.

The outbreaks of avian influenza in Asia have highlighted several gaps in global disease surveillance that the U.S. must help address to improve our ability to prepare for an influenza pandemic. These limitations include (1) a lack of infrastructure in many countries for in-country surveillance networks; (2) the need for better training of laboratory, epidemiologic, and veterinary staff; and, (3) the resolution of longstanding obstacles to rapid and open sharing of surveillance information, specimens, and viruses among agriculture and human health authorities in affected countries and the international community.

In the past year, CDC and DHHS have made significant progress toward enhancing surveillance in Southeast Asia. However, this initiative needs to continue at both national and international levels if we are to sustain our progress, expand geographic coverage, and develop an adequate capacity to conduct effective surveillance. These efforts at building international as well as domestic surveillance are essential for detecting new influenza virus variants

earlier and making informed vaccine decisions for inter-pandemic influenza. With the ever-present threat of the emergence of a new pandemic strain, we need to know what is happening in commercial poultry farms and the family backyard flocks of Southeast Asia, as well as elsewhere throughout the world.

Recently, Congress passed and the President signed an FY 2005 Emergency Supplemental Appropriations Act for Defense, the Global War on Terror, and Tsunami Relief, which included $25 million in international assistance funds to prevent and control the spread of avian influenza in Asia. These funds will support disease surveillance among humans, laboratories, and training on avian influenza laboratory and field techniques in Asia. They are being provided both to the region of Southeast Asia and to six specific nations where human and/or animal disease is greatest. Funding will support the planning and preparedness needed to enable each country to carry out a rapid response in a more organized manner. National long-term planning is also necessary for these countries; therefore they must also strategically apply to non-governmental organizations for additional funds to complete their preparedness efforts. Funds are also being provided for three countries, Cambodia, Laos, and Vietnam, to conduct active case detection of human disease, and additionally to Burma, China, and Indonesia for detection of animal disease. With respect to Burma, any avian flu assistance activities would be channeled through international non-governmental organizations or be conducted by international health organizations and not through the Burmese government. We will be happy to brief Congress on the

specific activities that will involve Burma. Improved laboratories, including addressing biosafety for animal and human specimens will be the initial focus. Better in-country communications will be developed to assist these populations to taking steps to prevent infection and disease. Direct assistance to Vietnam will provide technical help for the safe development of an H5N1 vaccine. Finally, rapid response teams for Vietnam, Cambodia, and Laos will be organized and trained to respond to a crisis by identifying disease and instituting quarantine, isolation, and any other control measures that are necessary. These teams will be supplied with materials to be stockpiled in Southeast Asia, so that they will be equipped with proper personal protective equipment when they conduct case investigations.

On the domestic side, during the past year, CDC has considerably improved surveillance in this country by working with the Council for State and Territorial Epidemiologists (CSTE) to make pediatric deaths associated with laboratory confirmed influenza nationally notifiable, and by implementing hospital-based surveillance for influenza in children at selected sites. CDC will continue to work with CSTE to make all laboratory confirmed influenza hospitalizations notifiable. Since 2003, we have issued interim guidelines to states and hospitals for enhanced surveillance to identify potential H5N1 infections among travelers from affected countries, and these enhancements continue. CDC also has been holding special laboratory training courses to teach state laboratory staff how to

use molecular techniques to detect avian influenza. CDC has trained professionals from all 48 states that desired training.

In addition, we are working to: (1) ensure that states have sufficient epidemiologic and laboratory capacity both to identify novel viruses throughout the year and to sustain surveillance during a pandemic; (2) improve reporting systems so that information needed to make public health decisions is available quickly; (3) enhance systems for identifying and reporting severe cases of influenza; (4) develop population-based surveillance among adults hospitalized with influenza; and, (5) enhance monitoring of resistance to current antiviral drugs, to guide policy for use of scarce antiviral drugs.

Managing the Vaccine Supply

During an influenza pandemic, the presence of influenza vaccine manufacturing facilities in the U.S. will be critically important. The pandemic influenza vaccines produced in other countries are unlikely to be available to the U.S. market, because those governments have the power to prohibit export of the vaccines produced in their countries until their domestic needs are met. The U.S. vaccine supply would be particularly fragile; only one of three influenza vaccine manufacturers selling vaccine in the U.S. market makes its vaccine entirely in the U.S.

In the U.S., public demand for influenza vaccine varies on a yearly basis, but having a steadily increasing demand would provide companies with a reliable, growing market that would be an incentive to increase production. In FY 2006, DHHS and CDC have provided $40 million in new funds for purchasing influenza vaccine for the pediatric stockpile to protect against annual outbreaks of influenza, and $30 million for contracts to expand the production of bulk single-strain influenza vaccine for use if needed during annual influenza seasons or possibly in a pandemic situation. In addition, the President is requesting $120 million in FY 2006, an increase of $21 million, to encourage greater production capacity that will enhance the U.S.-based vaccine manufacturing surge capacity to help prepare for a pandemic and further guard against annual shortages.

DHHS also appreciates the inclusion of $58 million in the FY 2005 Emergency Supplemental to procure additional influenza countermeasures for the CDC Strategic National Stockpile (SNS) in FY 2005. At present, the H5N1 viruses isolated from people in Asia during the past two years appear resistant to one class of antiviral drugs but sensitive to oseltamivir (Tamiflu). Accordingly, the SNS has stockpiled enough oseltamivir (Tamiflu) capsules to treat approximately 2.26 million adults and oseltamivir (Tamiflu) suspension to treat nearly 110,000 children. With the increased funding, CDC plans to purchase an additional 2 million regimens of oseltamivir. In addition, SNS funds have been used to purchase approximately 2 million bulk doses of unfinished, unfilled H5N1

vaccine. This vaccine has not yet been formulated into vials, nor is the vaccine licensed. Clinical testing to determine dosage and schedule for this vaccine began in April 2005 with funding from the National Institutes of Health. Additionally, DHHS also is supporting the development and testing of potential dose-sparing strategies that potentially could allow a given quantity of vaccine stock for use in more people.

One of the main efforts by CDC is to expand the nation's use of influenza vaccine during inter-pandemic influenza seasons. This increase will help assure that the U.S. is better prepared for a pandemic. Influenza vaccine demand drives influenza vaccine supply. Therefore, if we can increase annual vaccination efforts, we will increase annual production efforts, which help strengthen our capacity for vaccine production during a pandemic. Discussions are under way to review the studies that would be needed to consider broadening recommendations for influenza vaccination. CDC also is developing strategies to increase influenza vaccine demand and access by persons who are currently recommended to receive vaccine each year. For example, according to a 2003 Institute of Medicine report, there are approximately 8.2 million uninsured adults 18-64 years with high-risk conditions warranting vaccination against influenza. If such persons receive influenza vaccine, it will help to increase annual demand for vaccine, because one of the best predictors of being vaccinated is having been vaccinated in a previous season. This increase in annual demand will lead

to increased production capacity, and thereby increase vaccine supply both annually and during a pandemic.

Additionally, for planning purposes, CDC has identified influenza vaccine supply scenarios that may occur in future influenza seasons. These scenarios range from worst-case to best-case situations and are an important part of CDC planning efforts. We are preparing recommendations, plans, and communication messages for each of these possible situations.

Conclusion

Although the present avian influenza H5N1 strain in Southeast Asia does not yet have the capability of sustained person-to-person transmission, we are concerned that it could develop this capacity. CDC is closely monitoring the situation in collaboration with the World Health Organization and the affected countries. CDC is using its extensive network of partnerships with other federal agencies, provider groups, non-profit organizations, vaccine and antiviral manufacturers and distributors, and state and local health departments to enhance pandemic influenza planning. Our responses to the annual domestic influenza seasons provide the core foundation for how the nation will face and address pandemic influenza.

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

Chairman TOM DAVIS. Thank you.
Dr. Fauci.

STATEMENT OF DR. ANTHONY S. FAUCI

Dr. FAUCI. Thank you very much, Mr. Chairman and members of the committee, for allowing me to discuss with you this morning the role of the NIH research endeavor in the ultimate development of countermeasures against pandemic flu in the form of diagnostics, therapeutics and vaccines.

Very briefly to put this into perspective, this slide here on your left shows the complementary roles within the Department of Health and Human Services. You have just heard from Dr. LeDuc about the CDC's role in surveillance, detection, disease control and prevention. The NIH, as I will outline briefly for you, conducts basic and clinical research ultimately to develop vaccines and therapeutics. There is an important role for the FDA in the regulatory process of the approval of these products. This is all coordinated under the Office of Public Health Emergency Preparedness.

Next slide. The research enterprise at NIH is based fundamentally as are all of our projects on sound basic research that we hope to rapidly apply to the clinical setting of developing in this case vaccines and therapeutics. We do a bit of surveillance and epidemiology at the molecular level to look at the evolution of the virus, but the surveillance is fundamentally the responsibility of the Centers for Disease Control and Prevention.

I am going to give you a couple of examples of some of the basic and clinical research that is done, if I could have the next slide. You may have heard of the terminology "reverse genetic system." This is a system of being able to much more accurately and consistently develop seed viruses for vaccines.

It may appear to be somewhat complicated, but it really is very simple. When we have a virus that we isolate, for example, in Asia that we want to make a vaccine for, we generally co-grow it with a strain that we know works well in eggs and that we have a great deal of experience with. During that process, the genes re-assort and ultimately give us a good growing, but nonetheless specific virus.

Reverse genetics deliberately takes the appropriate genes from each of those strains and re-combines them in a proactive way to take away the uncertainty. In fact, the vaccine that I am going to mention in a moment, the H5N1, was isolated and developed into a seed virus using reverse genetics technique. Next slide.

In addition, we, together with the CDC and in collaboration with several of the pharmaceutical companies, are working to make the transition from the egg-based system of developing a vaccine for influenza to a cell-based culture. The reasons for that are several, but the most important of which is the greater surge capacity of the cell-based system to be able to make more doses on a shorter notice, as well as to change direction if in fact we have a surprise virus that comes upon us. Next slide.

Probably the most important component of what we do relates to the actual clinical trials and testing of the vaccine in question. I must say that in fact we have been the first and are still way ahead of the rest of the world in the development of an H5N1 vac-

cine that is taking place in our clinical trial sites in this country to determine safety and the correct dose. Next slide. Very briefly, the H5N1 inactivated virus trial was started on April 5, 2005. We have completed the first two stages on 450 people. The dosage data, it will be done in multiple doses and in a prime boost will be available for analysis by mid-July. The safety data will be available for analysis by mid to end of August.

In addition, we are doing an attenuated vaccine trial that is planned for late 2005 for the H5N1. We are also studying another bird flu that is not as ominous as the H5, but nonetheless important, and that is the H9N2.

With regard to therapy, we have an anti-viral screening program. There are two major classes of drugs. The amantadine group, unfortunately the H5N1, that is circulating in Asia now is resistant to that. We can talk about why that might be the case during the question period. The other is the group that is the neuraminidase inhibitors, including Tamiflu. We are also looking for other alternative targets, as well as looking at how to use these drugs in combination where there are resistant scenarios, in addition to how to best use these drugs in different categories of patients.

On the final slide, let me just summarize that the NIH's effort is fundamental research, as I mentioned. It is all geared to the rapid and expeditious development of the important countermeasures that are needed to counter a pandemic flu.

I would be happy to answer questions during the question period. Thank you, Mr. Chairman.

[The prepared statement of Dr. Fauci follows:]

Testimony
Committee on Government Reform
United States House of Representatives

The Role of NIH Biomedical Research in Pandemic Influenza Preparedness

Statement of
Anthony S. Fauci, M.D.
Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
U.S. Department of Health and Human Services

For Release on Delivery
Expected at 10:00 AM
Thursday, June 30, 2005

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 preparing the Nation for the next influenza pandemic. The Department of Health and Human Services (DHHS) Draft Pandemic Influenza Preparedness and Response Plan outlines a coordinated national strategy to prepare for and respond to an influenza pandemic, and assigns specific roles to various Federal agencies; the National Institute of Allergy and Infectious Diseases (NIAID) holds the primary responsibility for carrying out those duties assigned to NIH.

In this capacity, NIAID provides the scientific input required to facilitate the development of both new influenza vaccine technologies and novel antiviral drugs against influenza viruses. Under this Administration, we have made extraordinary progress. DHHS has been investing in new technologies, securing more vaccines and medicines, and preparing stronger response plans. Total NIH funding for influenza research has grown more than five-fold in recent years, from $20.6 million in FY 2001 to an estimated $119 million in FY 2005. This is part of the largest investment ever made by the Federal government in protecting against influenza.

Influenza epidemics typically occur during the winter months in the United States and other temperate regions of the world and cause significant morbidity and mortality. On average, 36,000 people in this country die each year and 200,000

are hospitalized due to influenza and influenza-related complications. Each year, influenza viruses undergo small changes in their surface proteins as they circulate through the human population. As these small changes accumulate, the influenza virus gains the ability to overcome immunity created by prior exposure to older circulating influenza viruses or by vaccination. This phenomenon, called "antigenic drift," is the basis for the well-recognized patterns of influenza disease that occur every year, and is the reason that influenza vaccines must be updated each year.

Influenza viruses also can change more dramatically; viruses may emerge that can jump species from natural reservoirs such as wild ducks to infect domestic poultry, farm animals, or humans. This type of significant change in the antigenic makeup of the virus that infects humans is referred to as "antigenic shift."

In most instances when an influenza virus jumps species from an animal such as a chicken to infect a human, the result is a "dead end" infection that cannot readily be transmitted further from human to human. Mutations in the virus, however, could increase the efficiency of human-to-human transmission. Furthermore, if an avian influenza virus and another human influenza virus were to simultaneously co-infect a person, the genes of the two viruses might reassort, resulting in a virus that is readily transmissible between humans and against which the population would have no natural immunity. Such a virus could potentially cause an influenza pandemic.

Historically, pandemic influenza is a proven threat. Three influenza pandemics have occurred in the 20th century: in 1918, 1957, and 1968. The 1918-1919 pandemic was by far the most severe, killing over 500,000 people in the United States and 20-40 million people worldwide—almost two percent of the global population at that time. Worldwide, the pandemics that began in 1957 and 1968 killed approximately 2 million and 700,000 people, respectively.

H9N2 and H5N1 influenza are two avian viruses that have jumped directly from birds to humans and have significant pandemic potential. In 1999 and 2003, H9N2 influenza caused illness in three people in Hong Kong and in five individuals elsewhere in China, but the virus did not spread from human to human. H5N1 influenza, often referred to as "bird flu," appears to be a significantly greater threat than H9N2. This virus was first detected in humans in Hong Kong in 1997. Since January 2004, it has spread widely among wild and domestic birds and has infected at least 107 people in Vietnam, Thailand, and Cambodia; 54 of these people have died of the disease. Ominously, H5N1 viruses are evolving in ways that increasingly favor the start of a pandemic, including becoming more stable in the environment and expanding their host species range. Moreover, there have been 2 highly probable cases of human-to-human transmission of the H5N1 virus, and it is possible that other such transmissions have occurred recently.

The deadly experience with past influenza pandemics explains our current high level of concern about the appearance of virulent H5N1 avian influenza viruses in

Asia, which by a variety of mechanisms could adapt themselves to efficiently spread from human to human and result in the next 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.

NIH Influenza Research Activities

Between influenza pandemics, when influenza activity occurs regularly on a seasonal basis, the role of NIAID is to conduct basic research into the viral biology, pathogenesis, and epidemiology of influenza viruses and to study host immune responses to these agents. Concomitant with these basic research studies, NIAID conducts applied research to develop new or improved influenza vaccines and production methods; to identify new anti-influenza drugs; and to support surveillance for previously unknown influenza viruses in animals and characterize any that are found. When a new influenza virus begins to infect humans (and thereby gains the potential to cause a pandemic), NIAID's role is to develop and clinically evaluate specific candidate vaccines against the emergent strain, assess the virus's sensitivity to antiviral drugs, and, in some cases, supply vaccine manufacturers and the research community with viral reference strains and other reagents to speed vaccine development.

Basic Research

NIAID supports many basic research projects intended to increase our understanding of how influenza viruses replicate, interact with their hosts,

stimulate immune responses, and evolve into new strains. Results from these studies lay the foundation for the design of new antiviral drugs, diagnostics, and vaccines, and are applicable to seasonal epidemic and pandemic strains alike.

NIAID also supports two special research programs to better understand the diversity of influenza viruses. The Influenza Genome Sequencing Project, launched in the fall of 2004, is a collaboration between NIAID, the Centers for Disease Control and Prevention (CDC) and several other organizations to determine the complete genetic sequences of thousands of influenza virus isolates and to rapidly provide these sequence data to the scientific community. This program will enable scientists to better understand the emergence of influenza epidemics and pandemics by observing how influenza viruses evolve as they spread through the population and by matching viral genetic characteristics with virulence, ease of transmissibility, and other clinical properties. As of June 8, 2005, 206 genomic sequences of influenza viruses had been made available through this program to researchers via the NIH website, and many more are in the pipeline.

NIAID also supports a long-standing program based in Hong Kong to detect the emergence of influenza viruses with pandemic potential. This program, led by Dr. Robert Webster of St. Jude Children's Research Hospital in Memphis, Tennessee, conducts extensive surveillance of influenza viruses in animals in Hong Kong, analyzes new influenza viruses when they are found, and helps to

generate candidate vaccines against them. In January 2005, the scope of this surveillance program was expanded to include Vietnam, Thailand, and Indonesia.

Vaccines

Vaccines are essential tools for the control of influenza. NIAID supports numerous research projects and other initiatives to foster the development of new influenza vaccine candidates and manufacturing methods that are simpler, more reliable, yield more broadly cross-protective products, and provide alternatives to the egg-based technology currently used to grow the vaccine viruses.

In the Fiscal Year 2006 budget request, DHHS has requested $120 million to support pandemic influenza preparedness activities. These activities build on previous initiatives that include making chicken eggs available year round to provide for a secure supply and surge capacity for vaccine production and supporting efforts to shift vaccine manufacture to new cell-culture technologies. Moreover, a technique developed by NIAID-supported scientists called reverse genetics allows scientists to manipulate the genomes of influenza viruses and to transfer genes between viral strains. This technique allows the rapid generation of vaccine candidate strains that precisely match a selected epidemic strain. By removing or modifying certain virulence genes, reverse genetics also can be used to convert highly pathogenic influenza viruses into vaccine candidates that

are safer for vaccine manufacturers to handle. Other strategies for influenza vaccines, including protein subunit and gene-based vaccines, also are being actively pursued. For example, on the NIH campus in Bethesda, the NIAID Vaccine Research Center (VRC) has initiated a program to develop gene-based vaccines against influenza. Should proof-of-concept studies prove successful, the VRC expects to expand and accelerate the development of gene-based and recombinant influenza vaccines.

In addition to supporting the development of new vaccine strategies, NIAID maintains an extensive capacity for evaluating candidate vaccines in clinical trials. For example, NIAID's Vaccine and Treatment Evaluation Units (VTEUs) comprise a network of university-based research medical centers across the United States that conduct clinical trials to test candidate vaccines for many infectious diseases. These units support both academic and industrial vaccine evaluation, including safety, immunogenicity, and ultimately, efficacy of candidate vaccines.

Although a pandemic alert has not yet been declared, NIAID has taken a number of steps to develop and clinically test vaccines against H5N1 and H9N2 influenza, two specific avian viruses that, as noted above, have significant pandemic potential. For example, in August 2004, NIAID contracted with Chiron Corporation for the production of 40,000 doses of an inactivated H9N2 vaccine.

A Phase I clinical trial of this vaccine in adults began on March 31, 2005, and is fully enrolled.

In January 2004, researchers at St. Jude Children's Research Hospital obtained a clinical isolate of the highly virulent H5N1 virus that continues to be fatal to humans in Vietnam and used reverse genetics to create an H5N1 vaccine candidate from this strain. After NIAID received this vaccine candidate last June, it was sent immediately to Sanofi-Pasteur (formerly Aventis-Pasteur) and shortly thereafter to Chiron. These companies have NIAID contracts to manufacture pilot lots of eight and ten thousand vaccine doses, respectively. The inactivated H5N1 vaccines will be tested in Phase I and II clinical trials that will assess safety and the appropriate vaccine dosage to optimize immunogenicity, as well as provide information about how the immune system responds to this vaccine. The Sanofi-Pasteur trial, which began on April 4, 2005, is testing the vaccine in approximately 450 healthy adults between the ages of 18 and 64. This trial is already fully enrolled. If data from this study indicate the vaccine is safe and able to stimulate a potentially protective immune response, NIAID expects to test the vaccine in other populations, such as the elderly and children, in late summer 2005. Trials of the Chiron-produced vaccines are expected to begin later this year.

In addition to these relatively small pilot lots, DHHS contracted with Sanofi-Pasteur to produce two million doses of its H5N1 vaccine, in order to ensure that

the manufacturing techniques, procedures, and conditions that would be used for large-scale production will yield a satisfactory product. Moving to large-scale production of the vaccine in parallel with clinical testing of pilot lots is an indication of the urgency with which we have determined that H5N1 vaccine development must be addressed. Waiting for the results of the initial clinical trials, which would be the normal procedure, would delay our ability to make large quantities of vaccine by at least six months. These doses, which have now been manufactured, could be used to vaccinate health care workers, researchers, and, if indicated, the public in affected areas.

From the mid 1970s to the early 1990s, intramural and extramural NIAID researchers developed a cold-adapted, live attenuated influenza vaccine strain that later became the FDA-licensed influenza vaccine marketed as FluMist. Building on their experience with attenuated influenza vaccines, researchers from the same intramural laboratory involved in previous efforts recently made three candidate attenuated H5N1 vaccine strains and an attenuated H9N2 vaccine strain that are now in advanced development. NIAID plans to start the clinical trial of the attenuated H9N2 candidate vaccine this summer. These researchers also hope to test one of the candidate attenuated H5N1 vaccines in a Phase I study this year.

Antiviral Therapies

Antiviral medications are an important counterpart to vaccines as a means of controlling influenza outbreaks, both to prevent illness after exposure and to treat infection after it occurs. Four drugs are currently available for the treatment of influenza, three of which are also licensed for prevention of illness. NIAID actively supports identification of new anti-influenza drugs through the screening of new drug candidates in cell culture systems and in animal models. In the past year, seven promising candidates have been identified. Efforts to design drugs that precisely target viral proteins and inhibit their functions also are under way. In addition, NIAID is developing novel, broad-spectrum therapeutics that might work against many influenza virus strains. Some of these target viral entry into human cells, while others specifically attack and degrade the viral genome.

Efforts also are underway to test and improve antiviral drugs to prevent or treat H5N1 influenza. Last year, researchers determined that although H5N1 viruses are resistant to two older drugs—rimantadine and amantadine—they are sensitive to a newer class of drugs called neuraminidase inhibitors, including oseltamivir, which is marketed as Tamiflu and is approved for use in individuals older than one year. DHHS has deposited approximately 2.3 million treatment courses of oseltamivir in the Strategic National Stockpile, to which more doses will be added. Scientists are planning to conduct studies to further characterize the safety profile of oseltamivir for very young children; and studies are also in progress to evaluate novel drug targets, as well as long-acting next-generation neuraminidase inhibitors. In addition, development and testing in animals of a

combination antiviral regimen against H5N1 and other potential pandemic influenza strains are under way.

Conclusion

In closing, Mr. Chairman, I would like to emphasize that although we cannot be certain exactly when the next influenza pandemic will occur, we can be virtually certain that one will occur and that the resulting morbidity, mortality, and economic disruption will present extraordinary challenges to public health authorities around the world. We are working diligently in close coordination with our colleagues at CDC, FDA, other federal agencies, and in industry to ensure that we can meet these challenges in the most successful manner possible.

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

The Role of NIH Biomedical Research in Pandemic Influenza Preparedness

U.S. House of Representatives Committee on Government Reform

Dr. Anthony S. Fauci, M.D.
Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services
June 30, 2005

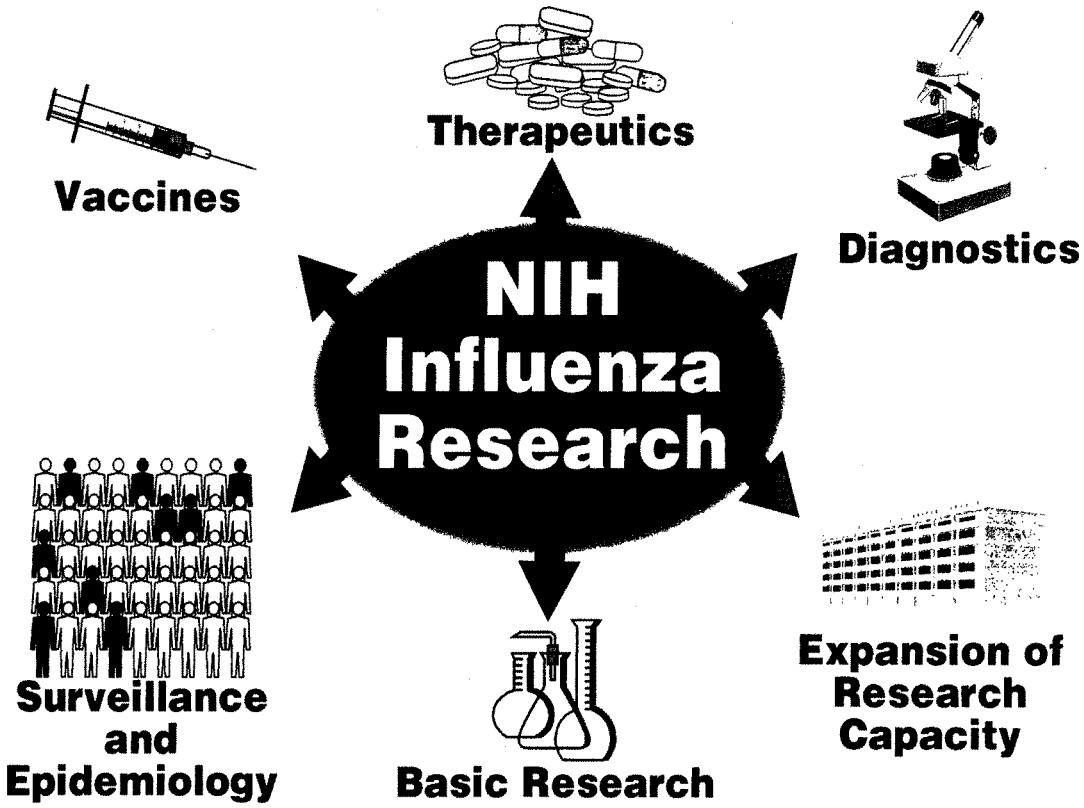
Pandemic Influenza Preparedness: Complementary Roles within DHHS

CDC
- Surveillance and detection
- Train local response teams
- Maintain vaccine/antiviral stockpiles
- Disease control/prevention

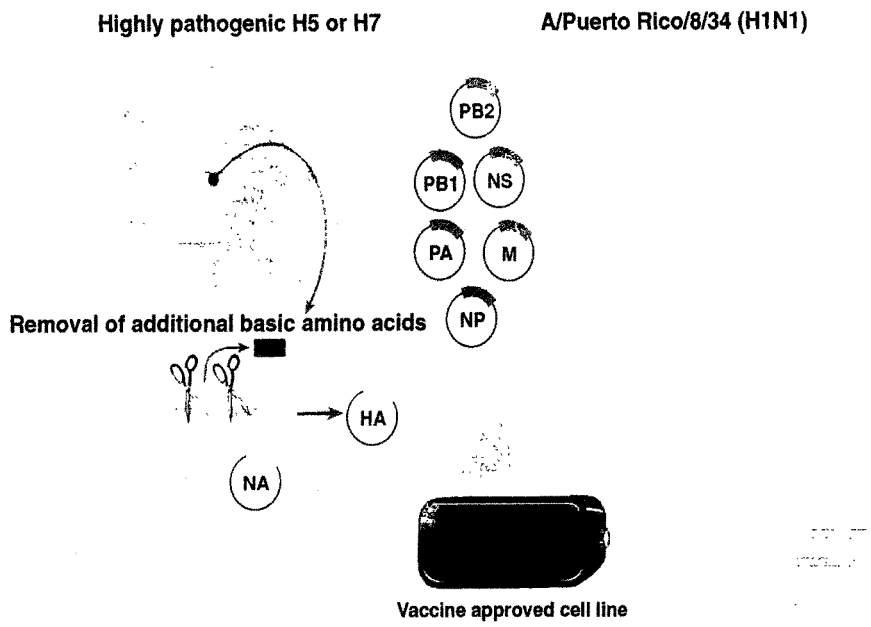
NIH
- Conduct basic research
- Develop medical interventions (vaccines, antivirals)
- Conduct clinical evaluation of vaccines and antivirals

FDA
- Regulatory approval – vaccines, therapeutics, diagnostics

OPHEP
- Office of Public Health Emergency Preparedness coordinates HHS-wide emergency preparedness activities

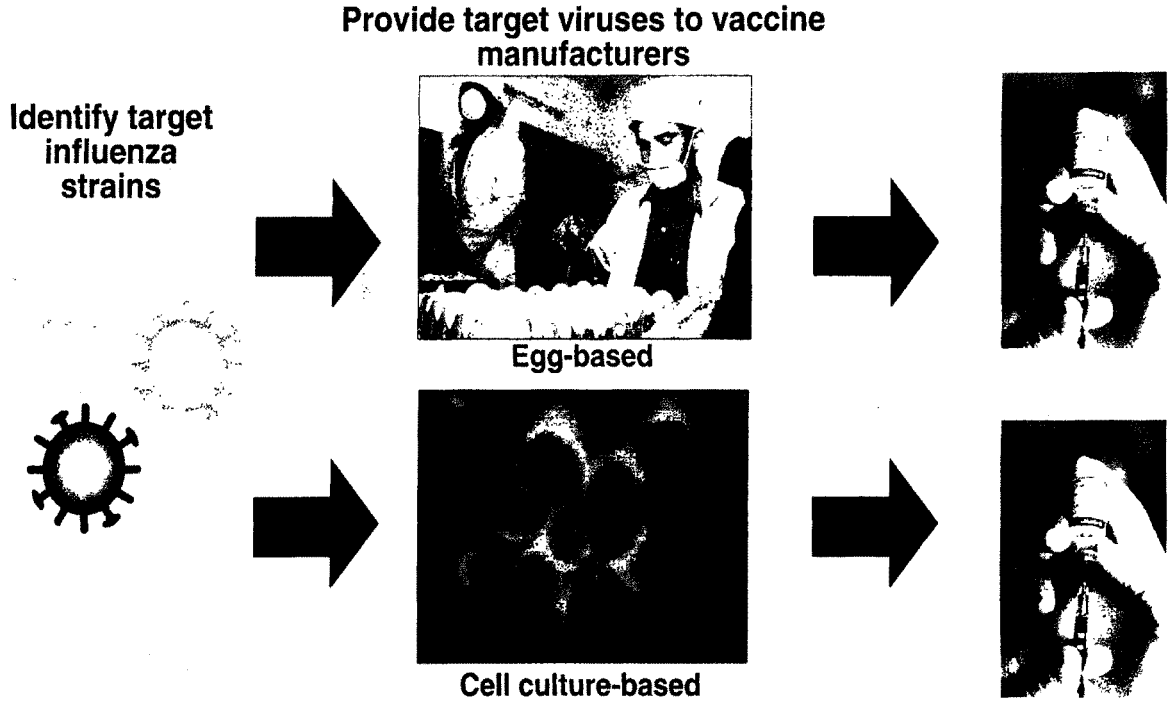

NIH
Influenza
Research
Vaccines
Therapeutics
Diagnostics
Surveillance
and
Epidemiology
Basic Research
Expansion of
Research
Capacity

Influenza Seed Virus for Inactivated Virus Vaccine Production Using a Reverse Genetics System



Source: Webster et al: *Vaccine* 20:3165 (2002); Science 302:1519 (2003)

Influenza Vaccine Production: Cell Culture as an Alternative to Chicken Eggs



Reuters
March 24, 2005

U.S. Starts Human Tests of Bird Flu Vaccine

Phase 1 trial on 450 adults will determine safety of shots

U.S. health officials said on Wednesday they have started human tests of a vaccine against avian flu, which experts believe could kill tens of millions of people if it becomes easily passed from person to person.

Clinical Trials for Pandemic Influenza

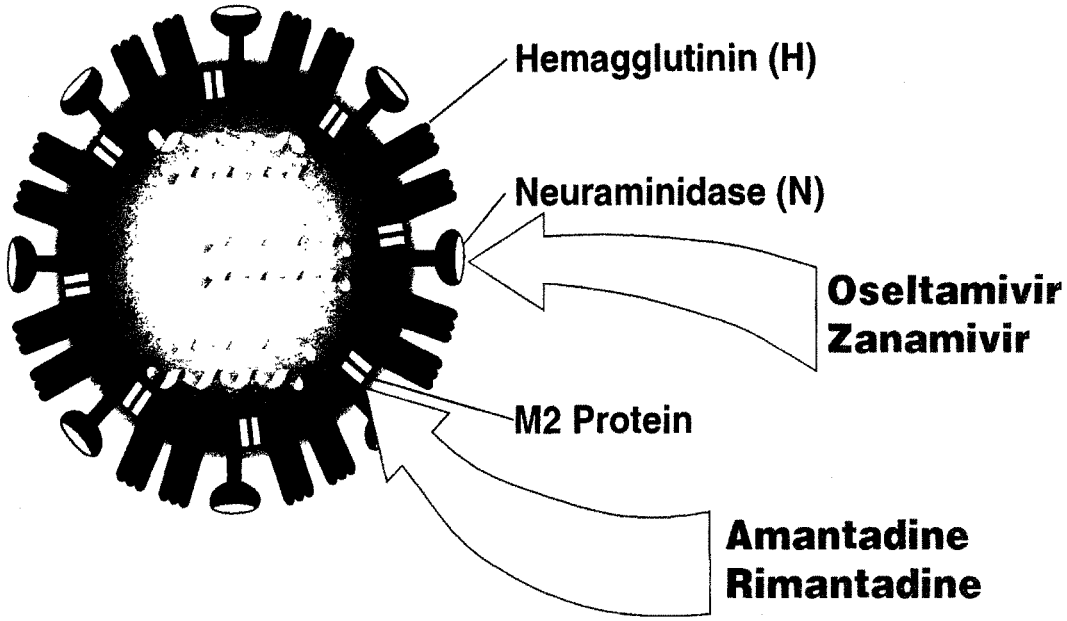
H5N1

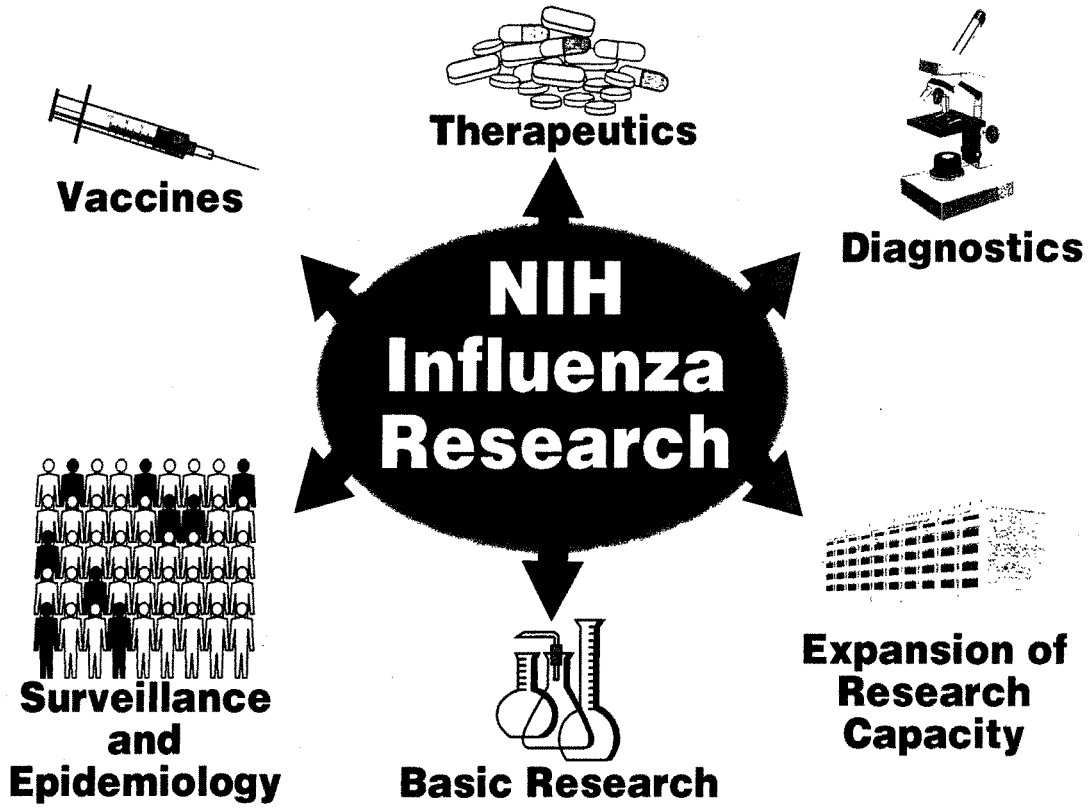
- Inactivated vaccine trial began April 4, 2005
  - Stage 1: fully enrolled (118 healthy adults)
  - Stage 2: fully enrolled (333 healthy adults)
  - Upon review of safety and preliminary immunogenicity data, plan to conduct trials in healthy elderly and children in late summer 2005
- Attenuated vaccine trial planned for late 2005

H9N2

- Inactivated vaccine trial began March 31, 2005
  - Fully enrolled (96 healthy adults)
- Attenuated vaccine trial planned for summer 2005

Antiviral Therapies for Influenza




NIH
Influenza
Research
Therapeutics
Diagnostics
Vaccines
Surveillance
and
Epidemiology
Basic Research
Expansion of
Research
Capacity

Chairman TOM DAVIS. Thank you very much.
Dr. Gellin.

STATEMENT OF DR. BRUCE GELLIN

Dr. GELLIN. Thank you, Mr. Chairman and members of the committee. I am pleased to have the chance to discuss with you this morning the department's involvement with avian influenza and the steps we are taking to prepare for a pandemic.

As you have mentioned in your remarks and you have heard from my colleagues this morning, many public health experts believe the threat of a pandemic is now greater than it has been in decades. A report by the World Health Organization warns that the H5N1 virus may be evolving in ways that increasingly favor the start of a pandemic.

The thin silver lining on this otherwise darkening cloud is that despite the wide geographic spread of the virus, despite its ability to infect an expanding number of avian and mammalian species, despite the small changes in the virus' genetics, and despite the occurrence of small clusters among people where transmission may have been person to person, this virus has not yet developed the ability to efficiently transmit among people, a change that could trigger a pandemic.

While we are all focused on the evolving H5N1 situation, as Dr. Fauci mentioned, it is the nature of this virus to evolve. Therefore, we need to be prepared for any of these viruses that could do a similar thing.

Because the emergence of a pandemic anywhere could lead to a pandemic everywhere, this indeed is a global issue. It is why the department has made preparedness for an influenza pandemic one of its highest priorities. It is why it is a critical component of Secretary Leavitt's 500-day plan. It is why Secretary Leavitt on his first international trip in May gave a plenary talk at the World Health Assembly, the annual meeting of the ministers of health around the world, and hosted a meeting of more than a dozen ministers of health in the affected region, reinforcing the need for global transparency, strengthened surveillance and communications, and timely sharing of information and clinical specimens.

It is also why Secretary Leavitt established a department-wide Influenza Task Force to coordinate all HHS activities affecting the public health preparedness for both seasonal influenza and pandemic. It is why HHS has made significant investments in adding influenza-specific medicines and vaccines to our strategic national stockpile, and why we are currently in active discussions with the manufacturers of these drugs and vaccines to obtain more.

It is also why we have supported the World Health Organization's global influenza effort through both human and financial resources, and why we provide technical assistance and other resources through a number of bilateral agreements with countries in the affected regions.

And it is why we have collaborative working relationships with many other parts of the U.S. Government, including the Department of Agriculture, the Department of State, the USAID, the Department of Defense and the Veterans Administration, to name a few.

And it is why Secretary Leavitt has asked that the department complete the updated 2005 pandemic preparedness and response plan. This plan describes a coordinated strategy to prepare for and respond to a pandemic. The updated plan will address the outstanding policy issues and provide the guidance and specificity that is needed by local and State health departments, the health care community, the public and the international community. We anticipate that we will be regularly revising and reworking the plan that incorporates evolving science and experience.

With the broad area of pandemic influenza, the department's priority areas include public health preparedness, surveillance, stockpiles of drugs and vaccines, vaccine development and advanced product development, and basic and applied research. Drs. LeDuc and Fauci have highlighted a number of these areas already, so in the few minutes that remain I would like to spotlight our approach to developing our armamentarium for pandemic antiviral drugs and vaccines.

As you know, last year we began to include anti-viral drugs in the strategic national stockpile. The bottom line is that today, neuraminidase inhibitor drugs are the only class of anti-virals that can take on this virus. It is worrisome that the other class, the M2 inhibitors or the adamantines are no longer effective. As recently reported in the Washington Post, it appears that the use of these anti-viral drugs in livestock feed are largely responsible for the emergence of resistance to this virus, underscoring the critical importance that these drugs be used appropriately so they will continue to work.

We are also exploring the potential to include other anti-viral drugs in our strategic national stockpile, including zanamivir, also known as Relenza. I would like to acknowledge our appreciation of Congress' inclusion of the $58 million supplement so that we could procure these additional countermeasures for our stockpile.

In addition to anti-viral drugs for the treatment and prevention of influenza, vaccination is one of the most important tools that we have for pandemic preparedness. It is important to acknowledge that the perfect vaccine cannot be prepared in advance and stockpiled since the vaccine needs to be tailored to match the circulating virus.

We have gone ahead, as Dr. Fauci mentioned, and created a vaccine and we have 2 million potential doses that have been made in bulk waiting for the result of the NIH trial to know what dose should be used. This provides us with some vaccine that has potential use and also provides at least one vaccine manufacturer with significant experience working with this strain in commercial-scale facilities.

HHS has developed several other influenza vaccine supply initiatives that are designed to secure and expand the influenza vaccine supply, diversify our production methods such as cell culture, and establish emergency surge capacity. To support these activities, HHS received $50 million in fiscal year 2004, $99 million in fiscal year 2005, and in the current President's budget, we have an additional $120 million to strengthen this component of our preparedness.

Our pandemic efforts include beyond the cell cultured vaccine that Dr. Fauci mentioned, efforts to improve the efficiency of the manufacturing process and approaches that could effectively stretch the number of vaccine doses by decreasing the amount of vaccine antigen in each dose. These dose-stretching strategies may be affected by the use of an adjuvant or administration such as interdermal administration.

While issuing the requests for proposals and completing the contracts is only the first step toward development of an expanded, diversified and strengthened vaccine supply, as Dr. Fauci mentioned, the United States is leading the global effort to develop vaccines and vaccine technologies to meet this challenge.

Thank you for our attention to my remarks, and I look forward to any questions you may have.

[The prepared statement of Dr. Gellin follows:]

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

Pandemic Influenza Preparedness

Statement of
Bruce G. Gellin, M.D., M.P.H.
Director,
National Vaccine Program Office
Office of Public Health and Science
Office of the Assistant Secretary for Health
U.S. Department of Health and Human Services

National Vaccine Program Office

For Release on Delivery
Expected at 10:00 AM
Thursday, June 30, 2005

Mr. Chairman and members of the Committee, I am Dr. Bruce Gellin, Director of the National Vaccine Program Office at the Department of Health and Human Services and the Chair of the Secretary's Influenza Preparedness Task Force. I am pleased to appear before you today to discuss avian influenza and the measures the Department is taking to prepare for an influenza pandemic.

An influenza pandemic is a global outbreak of disease that occurs when a new influenza A virus emerges in the human population, causes serious illness, and then spreads easily from person to person worldwide. Three influenza pandemics have occurred during the 20th century. The most deadly influenza pandemic outbreak was the 1918 Spanish flu pandemic, which caused illness in roughly 20 to 40 percent of the world's population and resulted in at least 500,000 deaths in the United States and 20-40 million deaths worldwide.

Many public health experts believe the threat of a pandemic is now greater than it has been in decades. A report issued by the World Health Organization warns that the virus may be evolving in ways that increasingly favor the start of a pandemic. In addition, the ecology of the disease and behavior of the virus have changed and are creating multiple opportunities for a pandemic virus to emerge. This is in large part because of the influenza H5N1 virus, the so-called "bird flu" that is established and endemic in many different species of birds in Asia. As these avian viruses continue to evolve and spread in animals, the possibility increases that an avian virus will recombine with a human virus to cause a novel and easily transmitted influenza virus strain in humans. Based on data that has

been made available to the World Health Organization on the impact of the H5N1 virus in Asia, more than half of the people who are known to have been infected with this virus have died from this infection. This is not an exact estimate of the mortality rate for this disease because only people who have become sick enough to go to the hospital have actually been diagnosed with the infection. There may be many more people who were infected without being diagnosed.

While scientists in 1918 had very little idea of what was happening until it was too late, we have time - and still have time - to prepare for the next global pandemic, and we should consider ourselves warned. As Secretary Leavitt stated at the World Health Assembly in May, "We are working on pandemic preparedness on borrowed time. When this event occurs, our response has got to be immediate, comprehensive and effective."

The Department has made preparedness for an influenza pandemic one of its highest priorities and it is a critical component of Secretary Leavitt's 500-day plan. In May, at the World Health Assembly -- the annual meeting of Ministers of Health from around the world -- the Secretary spoke of the Department's commitment in this area. He encouraged global transparency, strengthened surveillance and communications, and timely sharing of information and clinical specimens as a critical component of our global preparedness. Secretary Leavitt also urged international collaborations among developed and developing countries to control the virus among humans and animals. Further, the World

Health Assembly passed a resolution on pandemic preparedness that was originally offered by the U.S. as a blueprint for global action.

We have expanded and enhanced the planning and preparedness activities that are critical to improving the effectiveness of a national and worldwide response that would decrease the impact of a pandemic should it occur. HHS has increased support for pandemic influenza activities and is engaged in several efforts to enhance the nation's preparedness for such an outbreak. HHS supports pandemic influenza activities in several key areas including: public health preparedness, research, vaccine development and production, antiviral stockpiling, and surveillance.

In addition, on the national front, the Department has been actively revising the draft Pandemic Influenza Preparedness and Response Plan that was issued last year 2004. This Plan describes a coordinated strategy to prepare for and respond to an influenza pandemic. The 2005 update of the plan will address many of the outstanding policy issues and provide the guidance to state and local health departments, the healthcare system, the public and the international community. HHS will regularly be revising and reworking the plan in order to provide current thinking and current science.

Earlier this month, Secretary Leavitt established a Department-wide Influenza Task Force to coordinate all HHS activities affecting the public health

preparedness for seasonal influenza outbreaks and an influenza pandemic. The Task Force's near term objective is to ensure completion of an updated pandemic plan. Long term objectives include an effective and efficient global surveillance network for outbreaks of influenza-like illness in humans and animals, and interoperable local, state, and federal government response plans for influenza outbreaks within the United States – including strategies and plans for effective coordination with response partners, public and private, and timely communication with the public.

To address the outstanding policy issues that will be incorporated into the Department's 2005 update of the Pandemic Preparedness and Response Plan, a joint working group of the National Vaccine Advisory Committee (NVAC) and Advisory Committee on Immunization Practices (ACIP) has been established to provide guidance to the Department. In addition to representatives from each of these federal advisory committees, working groups have had representation from public health and health care organizations, industry, federal agencies and other Departments. Next month, a joint meeting of NVAC and ACIP will review the findings of the working group and develop recommendations for prioritizing the use of pandemic vaccine and antiviral drugs.

In addition to the guidance embodied in the Department's Pandemic Influenza Preparedness and Response Plan, HHS is taking many proactive steps to prepare and plan for a pandemic. One of these critical elements is the inclusion

of antiviral drugs in the Strategic National Stockpile (SNS). Another component of our preparedness is ensuring sufficient domestic surge capacity for influenza vaccine production.

Influenza antiviral medications have long been used to limit the spread and impact of institutional influenza outbreaks. These drugs may serve an important role in stemming a developing pandemic and in treating patients early in their influenza infection, with greatest effect if the drug is administered within 48 hours of onset of symptoms. We plan to utilize antiviral drugs as one influenza countermeasure to help mitigate influenza impact. Laboratory analyses demonstrate that these drugs appear to have activity against the H5N1 influenza strains in Asia; however, we have limited data to date about their effectiveness in treating patients infected with this virus. To date, there are some anecdotal reports of human H5N1 infections that have advanced despite early treatment, but anecdotes are not data. We need better data from the field to guide our decisions.

It is worrisome that M2 inhibitors, one of only two classes of antiviral drugs for influenza is not likely to be useful in fighting the H5N1 virus. As reported recently in the Washington Post, it appears that the use of the antiviral drug amantadine (an M2 inhibitor) in livestock feed in Asia is responsible for the emergence of resistance to the virus. This underscores the critical importance that these drugs

be used appropriately so as not to induce further resistance by the virus and removing this drug from our armamentarium.

The bottom line is that today, neuraminidase inhibitor drugs are the only class of antivirals available that can take on this virus. The United States has ordered and received delivery of approximately 2.3 million treatment courses of the antiviral, oseltamivir (Tamiflu®), a neuraminidase inhibitor, for the SNS and is currently in active discussions with Roche, the maker of this drug, to increase our national reserve. In addition, we are exploring the potential to include the other antiviral drug in this class, zanamivir (Relenza®), in the SNS. The Department also appreciates Congress' inclusion of $58 million in the FY 2005 Emergency Supplemental Appropriations Act for Defense, the Global War on Terror, and Tsunami Relief to procure additional influenza countermeasures for our Strategic National Stockpile.

In addition to antiviral drugs for the treatment or prevention of influenza, vaccination is one of the most important tools we have for pandemic preparedness, as it is the primary means to prevent morbidity and mortality during an epidemic. Because a pandemic is by definition the introduction and spread of a novel strain, there are major implications for vaccine development.

- First, the majority of the population is likely to be susceptible. NIH's clinical studies on the H5N1 vaccine will be available in the coming weeks and will provide critical information about the immune response and safety

profile of this candidate vaccine. Because humans' immune systems have not encountered this novel virus before, we expect that two doses of a vaccine might be needed for effective immunity, but we will let the science speak for itself when the results of these clinical trails are available.

- In addition we need to ensure that we have adequate capacity to produce a vaccine once its proof of principle has been established. To this end, we recognize that modern transportation and trade are likely to rapidly accelerate the global spread of influenza. Given our experience with the infectiousness of influenza, we assume that an outbreak somewhere is very likely to become a health threat anywhere...and potentially everywhere. As a consequence, our planning assumption is that in the setting of a pandemic emergency, there will be worldwide demand for vaccine and therefore vaccine produced outside of the United States will not be available for domestic use.

From a preparedness perspective, it is important to acknowledge that that the perfect vaccine cannot be prepared far in advance and stockpiled, since the vaccine has to be tailored to match the circulating virus. In addition to the vaccine that has been developed for NIH's clinical vaccine trials, we have asked Sanofi Pasteur develop 2 million doses of H5N1 vaccine based on the virus that was in circulation in Asia last year. We don't yet know whether the H5N1 vaccine will provide protection against a pandemic strain that might emerge, but this action provides us with some vaccine that has potential use, while also providing

at least one manufacturer with significant experience working with this strain in commercial-scale manufacturing facilities and is likely to translate into time saved in the development of a pandemic vaccine should the need arise. It is possible that the pandemic virus will continue to evolve (drift), such that this vaccine could be a poor match for and have limited effectiveness against the circulating strain but we chose to take advantage of the narrow window of opportunity in the manufacturing cycle so that this vaccine could be made without interfering with the production of the annual influenza vaccine that is made in the same facility.

Developing and producing a pandemic vaccine is further compounded by a fragile vaccine supply system. This fragility was documented during the past influenza season, when one of the two large influenza vaccine manufacturers could not supply vaccine to the U.S. market. While we are optimistic that there are new influenza manufacturers coming to US market, these ongoing problems with annual influenza production highlight the need for greater diversification of the U.S. domestic production capacity and the parallel need to improve demand for a life-saving vaccine that remains underutilized.

All U.S. licensed influenza vaccines are developed from viruses that are grown in embryonated eggs in a process unique for influenza vaccine. Influenza vaccine manufacturing happens when a strain of the virus adapted to grow in eggs is injected separately into millions of fertilized eggs, which are subsequently incubated to allow the influenza virus to grow. These egg-grown viruses are

inactivated, purified, tested for potency, blended into the trivalent vaccine, and filled into syringes or vials. The number of influenza vaccine doses produced is limited by the capacity of the production facilities, the availability of embryonated eggs, the yield of influenza virus from each egg, and the length of time that manufacturing takes.

HHS has developed several influenza vaccine supply initiatives to address annual as well as pandemic influenza vaccine. The objectives of these initiatives are to

- secure and expand U.S. influenza vaccine supply
- diversify production methods, and
- establish emergency surge capacity.

To support these activities, HHS received $50 million in FY2004 and $99 million in FY2005. The President's Budget for FY2006 includes an additional $120 million to further strengthen this component of the overall pandemic influenza preparedness efforts.

Because influenza vaccine is produced to meet the seasonal demand in the fall, production also is seasonal and embryonated eggs have not been available to manufacturers year-round. Moreover, although some excess supply may be available to support additional influenza vaccine production or provide security if the flocks that produce eggs for vaccine production are affected by avian influenza or other illness, this excess is limited creating vulnerability to supply

disruption. To enhance influenza vaccine supply security, HHS issued a five-year contract to Sanofi-Pasteur of Swiftwater, Pennsylvania, on September 30, 2004 for $40.1 million. Under this contract, Sanofi-Pasteur has begun to change its flock management strategy to provide a secure, year-round supply of eggs suitable for influenza vaccine production at full manufacturing capacity. It also will increase the number of egg-laying flocks by 20% to provide contingency flocks in case of an emergency. These eggs may be used to support additional production of annual influenza vaccine in the event of a vaccine shortage with the doses being delivered later in the fall. Additionally, this contract provides for production of annual investigational lots of prototype pandemic influenza vaccines. For example, this summer, Sanofi-Pasteur will manufacture an H7N7 virus vaccine that will be evaluated through the National Institutes of Health Vaccine Treatment and Evaluation Units.

Diversification of influenza vaccine production methods also will help strengthen the system. Cell culture technology is a well-established vaccine production method for other vaccines such as the inactivated poliovirus vaccine, and two companies have registered their cell-culture based influenza vaccine technology in Europe. This production technology does not require eggs as a substrate for growth of vaccine virus, thereby avoiding the vulnerabilities associated with an egg-based production system. It also may be more amenable to surge capacity production when influenza vaccine production will be needed to be expanded rapidly, such as at the time of a pandemic. Finally, the new cell-based influenza

vaccines will provide an option for people who are allergic to eggs and therefore unable to receive the currently licensed vaccines.

Earlier this spring, Secretary Leavitt announced that the Department of Health and Human Services issued a five-year contract on March 31, 2005 to Sanofi-Pasteur for $97.1 million to develop cell culture influenza vaccine technology and conduct clinical trials, with the goal of obtaining an FDA license for this vaccine. Under this advanced development contract, the company has also committed to manufacturing this vaccine at a U.S.-based facility with a capacity to manufacture 300 million doses of monovalent (single strain) pandemic vaccine over a one-year period. However, given timelines for vaccine development and clinical trials, and for construction and validation of manufacturing facilities, additional influenza vaccine supply from this source is unlikely to be available for at least five years.

These important steps to strengthen our national influenza vaccine supply through assuring the egg-supply and diversifying and expanding production capacity will be followed this year by additional measures to increase influenza vaccine production capacity and expand the number of influenza vaccine doses made using that capacity. Supported by the pandemic influenza vaccine initiative in the FY'06 budget request for $120 million, we posted synopses of three additional areas where we believe strategic investments move us toward achieving annual and pandemic influenza vaccine supply goals in the March 17, 2005 edition of FedBizOpps. On April 29, 2005, the first of these requests for

proposals was posted, providing support for the development of cell-culture based and recombinant pandemic influenza vaccines. This contract, leading to the licensure and U.S. production of a next-generation influenza vaccine, will further increase production capacity and diversification of the manufacturing base.

Whereas building new influenza vaccine production facilities is one approach to expand the influenza vaccine supply, other strategies also can increase the number of influenza vaccine doses produced. Influenza vaccine is manufactured in a series of steps – developing an influenza virus master seed for vaccine production, inoculating the virus into eggs, growing, harvesting, purifying, splitting, formulating, and filling it into vials or syringes. Improving efficiency at any step in this process can increase the eventual yield and number of vaccine doses produced. Thus, a second area of emphasis will be to support improvements of the manufacturing process to increase overall influenza vaccine production at current manufacturing facilities.

The third area of emphasis will provide support for research and development, leading to licensure of strategies that will stretch the number of vaccine doses produced by decreasing the amount of influenza virus antigen that is needed in each dose. The concept underlying these "dose-stretching" strategies is that by changing either the influenza vaccine or the way it is administered, one can improve the immune response to vaccination and provide protection while using

less of the vaccine antigen. By using less antigen in each vaccine dose, the number of doses that can be made at any level of production capacity would be multiplied. The two most promising antigen-sparing approaches are either to add an adjuvant (a substance that stimulates the immune response to a vaccine formulation), or administering the vaccine into the skin (similar to the approach used in a skin test for tuberculosis) where large numbers of potent immune cells are located. Both strategies have been evaluated in several clinical trials and have the potential to expand influenza vaccine supply several-fold if they prove effective in further clinical trials and are approved for licensure.

The increase in the FY 2006 President's Budget request will support ongoing activities to ensure that the Nation will have an adequate influenza vaccine supply to respond better to yearly epidemics and to influenza pandemics. While issuing the requests for proposals and completing the contracts is only the first step toward the development of an expanded, diversified, and strengthened influenza vaccine supply, the U.S. is leading the global effort to develop vaccines and vaccine technologies to meet this challenge.

Stemming the spread of the epidemic will require close coordination between the agriculture and health sectors and among affected countries, donor nations and international organizations dedicated to promoting the health of humans, livestock and wildlife. The FY 2005 Emergency Supplemental Appropriations Act for Defense, the Global War on Terror, and Tsunami Relief included $25 million

to prevent and control avian influenza in Southeast Asia. Detailed joint planning is already underway with the Department of State (with HHS focusing on human health) and USAID working (with USDA focusing on projects on animal health and related issues). In this way, the two agencies' plans will be complementary, not duplicative.

With this funding, we will support activities with the following goals:

- Strengthening the capacity of affected countries to conduct disease surveillance, prevention, and response, primarily in the most affected countries –Vietnam, Cambodia, and Laos
- Limiting the spread of the H5N1 avian influenza virus among birds.
- Limiting the spread of the H5N1 avian influenza virus from animals to humans.
- Reducing the potential economic consequences of avian influenza for affected countries.

The threat of a pandemic is real, whether it comes in 10 days or 10 years from now and whether it is H5N1 or another emerging strain. In anticipation of the next pandemic, we are working along with the global health community on this public health threat. The US has taken a leadership role in this area. We recognize the challenge before us, and know that we must all continue to be diligent and prepare for a potential public health threat of unimaginable magnitude.

Thank you for your attention to my remarks this morning – and more importantly to the attention that you have paid to pandemic influenza. I would be happy to answer any questions from the Committee.

Chairman TOM DAVIS. Thank you very much.

Dr. LeDuc, let me start. It is my understanding that we have two medical interventions for addressing a pandemic: a vaccine, which could take months to manufacture a sufficient quantity; or treatment with an anti-viral such as Tamiflu for those who get sick. At the moment, the United States has stockpiled only enough Tamiflu for 2 percent of the population. What, in your professional judgment, should be the level of the Tamiflu stockpile?

Dr. LEDUC. Clearly, Tamiflu has an important role to play in our national preparedness for the threat of pandemic influenza. It, however, is not our only resource. As you mentioned, vaccines are critically important. I think our strategy currently is to use antiviral drugs through the early phase during which a vaccine would actually be made. I think our efforts to actively engage in the global community to recognize early on the threat of pandemic influenza and to shorten the timeline between getting access to that virus and creating the new vaccine is also a factor in our considerations.

I do not have a number to give you. I would probably get in big trouble if I put forward a number anyway.

Chairman TOM DAVIS. That is why I am asking. [Laughter.]

But let me ask you, do we have enough?

Dr. LEDUC. No, we do not have enough. Clearly, we would like to have more. Perhaps Dr. Gellin or Dr. Fauci have better answers, but clearly we do not have enough.

Chairman TOM DAVIS. Dr. Fauci, do you agree with that?

Dr. FAUCI. Yes. We certainly do not have enough right now. We are well aware of that, which is the reason why we are in the process of negotiating to get more. What the right number is, Mr. Chairman, it really is very difficult, if not impossible, to give that. You have heard different groups who have estimated cover 50 percent of the population, cover 25 percent of the population. It is very difficult to determine what the right number is. I think the question you asked and the important point is that 2.3 million treatment doses is not enough and we have to get more, and that is the direction we are heading.

What problem we have is that the actual capacity to make it in a timely manner when you are having demands from other countries and other agencies throughout the world is also something that is problematic.

Chairman TOM DAVIS. Aren't other countries now trying to get more of this? That is I guess the point that you were trying to make.

Dr. FAUCI. Yes. So it makes it important for us to get our bid in now, yes.

Chairman TOM DAVIS. Dr. Gellin, would you agree with that?

Dr. GELLIN. I agree. Let me add to that that as I mentioned, we are in active discussions with all the companies that make all these products, both vaccines and anti-virals, because we are concerned about the capacity to manufacture surge capacity in the available supplies. You will likely hear from the drug company Roche in the second panel that they have recognized this, and after many discussions they have begun to develop a U.S. supply chain. So I think that part of what we are hearing about are many countries order-

ing in this case Tamiflu, but at the same time my understanding is that there is expanding capacity to make that drug.

I also mentioned in my brief remarks that we are also exploring the acquisition of the other neuraminidase inhibitor, zanamivir. It is a similar molecule. It has a slightly different set of clinical indications. It has given as an inhalation rather than oral. We think it is important to diversify that as well. It is more complicated to deliver that drug, but it is also important because of the potential emergence of resistance is that it potentially has a different resistance profile, so it would give us some backup.

Chairman TOM DAVIS. Dr. Fauci, currently FluMist, which is a nasal flu vaccine, is only approved for healthy children and adults from 5 to 49 years of age. As you know, we have talked about this before. Is there any research underway to consider the broader use of MedImmune's FluMist beyond the currently approved groups to help alleviate demand for injectable vaccines?

Dr. FAUCI. The answer is yes. We are in active discussions with the MedImmune people about trying to get the clinical information available to expand the usages of FluMist because it really is quite a good vaccine. It is a potent vaccine. It induces an even broader range of immunity than the kill dose. So it would behoove us to go in that direction and hopefully we will be able to do the appropriate studies to expand that usage beyond the current approval.

Chairman TOM DAVIS. Are there other anti-virals besides Tamiflu that might be effective against avian flu? Is NIH researching alternatives to Tamiflu or ways to speed up production of Tamiflu?

Dr. FAUCI. Currently, the neuraminidase inhibitors are the only drugs, anti-virals that appear to be effective against the H5N1. I mentioned in my statement just a few minutes ago of the resistance to the amantadine sub-group of M2 inhibitors which is the other class of anti-virals.

What we are doing in research, Mr. Chairman, is we are doing studies to try and determine if combinations of Tamiflu plus the amantadine in a resistant strain to amantadine might actually enhance the anti-viral effect. There is a good history in anti-viral drugs that when you have drugs to which a particular microbe are individually resistant and when you use them in combination, you get a pretty good effect. We see that with HIV and we see that sometimes in tuberculosis.

So we are doing those studies, and we are also doing studies to look at alternative targets. The two categories of drugs that I just mentioned are against two major targets: the M2 protein and the neuraminidase. We are looking at inhibition of entry of the virus, as well as other of the pathways in the replication cycle of the virus.

Chairman TOM DAVIS. Thank you.

Mr. Waxman.

Mr. WAXMAN. Thank you, Mr. Chairman.

The three witnesses before us are the good guys. They are trying to figure out what to do for our Nation against the threat of a pandemic flu, but I do not believe they are getting the support they need. Last fall, we had a severe shortage in flu vaccines. Our na-

tional health officials were caught completely unprepared. There were long lines for vaccines and widespread chaos and confusion.

When we examined what went wrong, we learned that the Department of Health and Human Services had ignored warning after warning that we were unprepared to cope with the vaccine shortage. Instead of leadership, our planning was characterized by complacency and false assurances.

So my question today is: Can we prevent the same fiasco from happening again? Dr. Gellin, in your testimony, well, you are the Director of the National Vaccine Program Office and Chair of the Secretary's Influenza Preparedness Task Force. Are we as prepared as we should be to face the threat of a pandemic?

Dr. GELLIN. Preparedness is not an absolute. I think it is clear to say that the efforts that have gone on even on my watch in my brief tenure as the Director of the National Vaccine Program Office have put us in a much better situation of preparedness. Not that I am responsible for those, but I think that it attests to much of what is going on. So there are clearly many more things that we can do and many things that we are doing, specifically around the vaccine piece.

Mr. WAXMAN. Let me ask you some questions about the plan.

Dr. GELLIN. Sure.

Mr. WAXMAN. You stated in your testimony that the department has been actively revising the draft pandemic preparedness and response plan. This is something that has been going on for a long time. As you acknowledge, the 2004 version of the draft contained many holes in key policy areas. Are you actively working to fix these key gaps? Will the new draft contain information on how vaccines will be purchased and distributed? Will the draft address prioritization of scarce supplies of vaccine and anti-viral drugs?

Dr. GELLIN. The clear answer to all those questions is yes. I think that it is important to recognize that the plan is not a skimpy outline. It is a fairly substantial document that we have put on our Web site for public comment last July. The areas you highlighted are specifically areas that we wanted the public to weigh-in on during the public comment period.

As Dr. LeDuc mentioned, we have involvement both from the Advisory Committee on Immunization Practices and the National Vaccine Advisory Committee to provide recommendations so that those critical policy issues can be answered. We cannot have a plan updated without those being addressed.

Mr. WAXMAN. Can you tell us a date by which this report will be released?

Dr. GELLIN. I cannot tell you a date. As mentioned before, it is our expectation that it will be released this summer. There are many moving parts to this and they are converging to the Secretary, who wanted to see it in early August. Subsequent to that, it is our hope to get that out shortly thereafter.

Mr. WAXMAN. Well, the States have been saying they are not getting adequate guidance from the Federal Government. I hope what you finalize will be much more thorough than last year's version.

Dr. GELLIN. As you mentioned in your introductory remarks, what we will have here is the specificity that the States are looking for so they can go on and make their own State-level plans.

Mr. WAXMAN. Dr. LeDuc, I appreciate your observation that the issues of pandemic influenza and annual influenza are linked. You noted that the same laboratories, the same health care providers, the same surveillance system and the same health department plans and personnel will guide both responses.

I would add that these factors link pandemic flu to many other public health issues, not just to annual flu epidemics. That is why I am so concerned the administration is proposing to cut support for local and State health departments by $130 million. The Secretary of the Washington State Health Department will testify in the next panel that these cuts are proposed at exactly the wrong time.

Why are we reducing the ability of State and local health departments to respond to a potential pandemic when health care experts say the risk of a pandemic are increasing? Given the threat of pandemic flu, would it be responsible for Congress to increase support of State and local health departments? I know you are not setting the funding priorities for the administration, but your concern over the pandemic flu should translate into more support for public health at HHS and in the White House.

In theory, public health is not a partisan issue. In practice, the funding of public health is more contentious, unfortunately, than it should be. What is your response?

Dr. LEDUC. Well, sir, I wholeheartedly support those comments. I could not agree more with your observations. I would just offer a hearty "yes, sir" that these are in fact very serious issues.

I think the threat of pandemic influenza, annual influenza, are just a few examples of the broader issue of emerging infectious diseases, many, many infectious disease threats that are facing the Nation. Clearly, we need a strong capacity at the State and local level to address these issues as a Nation.

Chairman TOM DAVIS. Thank you for your comments.

Mr. Gutknecht.

Mr. GUTKNECHT. Thank you, Mr. Chairman.

Let me just first of all disagree to a certain degree with my distinguished colleague from California, and let me make the point. The last several years, we have heard every year of this impending shortage of vaccine and the potential calamity that would follow thereon. I think in the last several years in every case it has proven not to be quite as serious as we thought.

I think we have to be careful of that. The reason I say that is that more and more the public, if you cry wolf too many times, the public does not take it very seriously. So I think we have to be careful as public policymakers to essentially say that there is a huge shortage out there; there is a huge public danger. I think there is a serious problem and I think we have to deal with it.

Just for my benefit and I think for the benefit of the American people, could you just in language that we can all understand explain the difference between an epidemic and a pandemic?

Dr. FAUCI. There are technical explanations, but in plain English, an epidemic is when you have a much greater than expected surge of cases within a particular defined geographic location. You could have an epidemic in a particular State or an epidemic in a particular region.

When you are talking pandemic, "pan" being "all," it is essentially all over the place, in plain English. That is really what a pandemic is.

Mr. GUTKNECHT. Let me come back to some other basics, just again so that I and others understand. What we are really worried about here are viruses that mutate and go from pigs to poultry to people or from poultry to pigs to people. Isn't that right?

Dr. FAUCI. Yes.

Mr. GUTKNECHT. And I am wondering, and the reason I am going to ask this question, I will tell you a little bit about two laboratories that I have in my district. One is a little medical practice that was started by a fellow by the name of William Worrall Mayo and his two brothers Will and Charlie. They have a pretty sophisticated laboratory there and they are doing some amazing things.

In fact, I was there a couple of months ago and they have a super-computer where they had taken the SARS virus and they showed the three-dimensional representation of the SARS virus, and they have actually tested using the computer the 10 most likely vaccines against the SARS virus, and have determined what they think would be the most viable.

The other is a little laboratory down in Worthington, MN run by some veterinarians. It is called Newport Labs. I will tell you the story, and the reason I tell the story is that what they do is they test animals. People will send cotton swabs in from around the country, and within 24 hours using very sophisticated, I think it is called PCR technology, they will determine what virus it is. More importantly, they will send back to them the right vaccine.

The reason I raise this question, and I think it is important that we continue to develop the vaccines and the other things, but what are we doing to try and, it seems to me if we could vaccinate the pigs and the poultry in Asia, maybe it is just a layman's view, but if we could keep the disease from ever becoming a pandemic, it would make some sense.

How much are we working with veterinarians and laboratories like that to try and stop the thing before it starts?

Dr. LEDUC. Let me start commenting. Dr. Fauci, I am sure, will have a lot to add.

First with regard to influenza in general, there are many strains and they actually exist in nature in wild birds. So there is basically a silent cycle and a silent reservoir of these strains. That is why Dr. Fauci pointed out that while H5N1 influenza is the current hot topic, we are also concerned about H9N2 and other strains. So there is this silent reservoir of circulating virus that is completely impossible to control.

The decision whether or not to immunize domestic animals as an amplifying host and a link to human transmission is often made on economic basis, in addition to the availability of an intervention of vaccine.

Unfortunately, we do not have the kind of ongoing dialog that we should have between the health sector and the agricultural sector. In an attempt to resolve this problem, we have actually assigned a person to WHO who comes from the agricultural sector. His sole job is to focus on influenza issues and establish a more robust dialog with the FAO and the OIE and WHO to try to approach a co-

ordinated response on how to integrate control both on the agricultural sector as well as the human health sector. So we are trying to work on this.

Dr. FAUCI. Just to add to that, to make sure we emphasize that is at the international level. We have good discussion and coordination. In fact, we just had a meeting yesterday at the White House with all of the parties involved, the Department of Agriculture included in that.

But from an international standpoint, I think the critical point that Dr. LeDuc made is it is so tied to the economies of the country that we are going to need a good deal of greater transparency in what is going on in those countries, and a willingness to assume some of the economic burdens and issues that will go along with appropriate culling, appropriate vaccination, getting a good vaccine.

One of the things we are worried about is that if you vaccinate some of the chickens, for example, with a partially effective vaccine, you may mask some smoldering infection. That is superimposed upon with what Dr. LeDuc said about the migratory birds being infected, which is very difficult to get a handle on. It is a very complex issue that at the level of WHO, working very close with the CDC and with the international counterparts, we are trying to address that. But it is a very difficult problem when you have economic considerations very closely tied with that.

Dr. GELLIN. If I could add, what you have described and what you have heard from my colleagues is really what is captured in the phrase "emerging infectious diseases," those that come out of the human-animal interface.

In addition to what Dr. LeDuc mentioned about some of the specific activities, there is also a supplement to the tsunami relief bill that is provided through the Department of State and HHS $25 million to focus on some of the strategic countries in Asia. One of the underlying focal points of that is to do as you described, to bridge the human and animal side so there is a common agenda.

Chairman TOM DAVIS. Mr. Cummings.

Mr. CUMMINGS. Let me followup on what Mr. Gutknecht said. I have a question, and something he said was chilling to me. Let me ask you this, gentlemen. In 2001, we had shortages of vaccine for children covering 8 of 11 others; 8 of 11 we did not have. Is that correct? And children died, did they not? Say yes or no, so I can hear you. I mean, it is for the record.

Dr. LEDUC. I believe that is correct, sir.

Mr. CUMMINGS. Children died.

In 2004, we had a shortage of flu vaccine and elderly people waiting in lines. Some of them actually died in line, and 36,000 people die each year from flu. Is that accurate? Come on, gentlemen.

Dr. LEDUC. That is correct, sir.

Mr. CUMMINGS. I am sorry?

Dr. LEDUC. That is correct, sir.

Mr. CUMMINGS. So my question is, do you think that we are crying wolf here? I mean, it is our responsibility as Members of the Congress to protect our citizens. I am just asking you, do you think we are crying wolf here?

Dr. FAUCI. No, but let me just add to what I think you are saying. We have discussed and we could reiterate, I certainly have at this committee in the past, and I mentioned it to the chairman as we were giving our statement, there is no doubt that the vaccine enterprise certainly in this country, and you used the word "fragile." You are absolutely correct. It is not only fragile. It is sort of broke, as it were.

The reason is that there is very little incentive to get vaccine companies involved in vaccine. We discussed this in light of the shortages. We have discussed this in the light of biodefense countermeasures that we need. We have a serious problem. So in that regard, I do not think you are crying "wolf." We have to fix the vaccine enterprise and make it such that consistently each year we have a predictable and supportable amount of vaccines.

Probably more broke than any of the vaccine sub-groups is the vaccine enterprise associated with influenza because it adds the seasonal uncertainty touch.

Mr. CUMMINGS. Let me ask you this. Dr. LeDuc, the Baltimore Sun recently reported "anti-viral drugs like Tamiflu are essential tool in slowing the spread of disease until a vaccine can be developed to immunize people, a process that can take six to 8 months from the time a killer virus is identified." Listen to this, "The United States has enough Tamiflu on hand for 2.3 million people," as you all have testified, "significantly less than some other nations. The United Kingdom, for example, has enough Tamiflu to treat 25 percent of their population, in accordance with the World Health Organization's recommendation."

What is the CDC doing to ensure the United States has enough anti-viral drugs to combat a pandemic and identify priority groups who will be most in need of that treatment? And why is it that other countries are able to cover a greater percentage of their people than we are? We have 36,000 people dying a year, and nine times as many people as who died on September 11th.

Dr. GELLIN. Let me get back to the heart of your question about the supplies in the stockpile and some of these materials. As I mentioned, and as Dr. Fauci mentioned, we have also been very aggressive about vaccine development. We see the need for both vaccines and anti-virals in the stockpile. You have heard in some detail about where we are going in the clinical trials, the going ahead and manufacturing 2 million doses, the request with manufacturers to make additional vaccine.

At the same time, we have actually bought and secured that amount of anti-viral in the stockpile. There will be subsequent purchases in the near future that are now under discussions with the companies, and additional purchases beyond that.

So it is important to recognize that we are not stopping at 2.3 million. As a point of fact, the other countries have put these other targets out there, not that it is a WHO recommendation per se, but they do not have much of a vaccine strategy right now so they have been putting more of their eggs in that anti-viral basket. We think that we need a balanced strategy as well, but I want to summarize by saying we are not stopping at 2.3 million. You will hear more in the near future about more and subsequently about additional purchases.

Mr. CUMMINGS. Before my time runs out, let me just ask you all this question. The Baltimore Sun recently reported about a pandemic flu simulation that occurred in my district, an affluent county, Howard County. A wide range of participants included representatives from the Governor's office and State and local public health officials.

The Sun reported, "It was not just the deaths in the scenario that disturbed them. Medical supplies were in short supply; absenteeism was soaring; police, firefighters, medical workers and air traffic controllers were among the thousands of sick, dead or terrified; hospitals and mortuaries were overwhelmed; the first small batches of the vaccine were arriving, but they were reserved for health care and public safety workers; crowds gathered demanding vaccination, and small riots were breaking out."

I just want your reaction to that, when we talk about our State and local folks, because they are on the front lines.

Dr. GELLIN. Indeed, they are on the front lines. I read that newspaper when it was on the stand. I think that depicts a number of the concerns about what a pandemic could do, which is why I believe that the plan will provide better guidance for the States as far as how they go about this, and the subsequent purchases of additional materials will help as well.

This all builds on the level of preparedness that has been encouraged by other funding, so I believe that these States are better prepared than they were before all this started.

Mr. CUMMINGS. Thank you, gentlemen.

Mr. SHAYS. Mr. Chairman.

Chairman TOM DAVIS. Yes, Mr. Shays.

Mr. SHAYS. Thank you.

I thank our witnesses again, and I thank you for holding this hearing.

I would like to know when does HHS propose to have a final version of a epidemic preparedness plan? Let me just throw these other questions out. Do you anticipate finalizing the plan before the 2005–2006 annual flu season? Are there practices and guidance in epidemic planning that are relevant should we experience another flu vaccine shortage this year?

Dr. GELLIN. Let me start with that. The plan, and I would be willing to loan you my copy of our draft plan, will be finalized this summer and it will include the specific guidance the States and localities are looking for. It will also include some of the strategic policy issues such as priority-setting when there are short supplies of vaccines and anti-virals. So all those will be done this summer in advance of the flu season.

Dr. LEDUC. If I could just add to that, actually this afternoon the ACIP is going to engage in discussions on the guidance on vaccine and anti-viral drug prioritization and their comments will then roll over to end back later on next month as well. So this really is a very timely discussion and we hope to have the final draft to the Secretary by the first of August. So we are moving along on this.

Mr. SHAYS. OK. Now, the draft plan only addresses HHS's activities. Correct? Yes. Given the broad nature of a pandemic and its impact on commercial agriculture, homeland security, and just society in general, does the administration have plans for government-

wide coordination and has anyone outside HHS been designated as the lead for orchestrating this coordination?

Dr. GELLIN. As Dr. Fauci mentioned just a few minutes ago, this coordination has been quite active. Within the Department of Health and Human Services, Secretary Leavitt sort of influenced the task force to deal with both pandemic influenza and annual influenza, given their relationships. There is a process that has really been coordinated by the White House to assure that there is broad input by all the departments that have a piece of this. I think in part it will also follow on to the national response plan for which there is likely to be a pandemic supplement.

Mr. SHAYS. One of the things that I am struck by is that Dr. Fauci when you said we just really do not know how many vaccines are the appropriate number. Is that correct?

Dr. FAUCI. I was referring to drugs, Mr. Shays.

Mr. SHAYS. OK.

Dr. FAUCI. I was asked what the right number of drugs was. We have 2.3 million treatment doses, and the question was what is the right number. I said clearly 2.3 million treatment doses is not enough.

Mr. SHAYS. What I am struck by, it seems to me by now we would almost have formulas that would come into play. First off, clearly this is the reason it is a pandemic, in that it is worldwide. Correct?

Dr. FAUCI. Right.

Mr. SHAYS. And obviously then we have a great deal at stake in what other countries do. The more vaccines that are out there worldwide, the less people in the United States will contract it. Correct?

Dr. FAUCI. Right, yes.

Mr. SHAYS. But isn't there a formula that tells you that?

Dr. FAUCI. The answer, Mr. Shays, is yes there are. There are mathematical models. The difficulty with the mathematical model as in all mathematical models, they are totally based on what the assumptions are that you put into the model. When you get predictions about how many people will get infected versus who will get sick, the range is enormous. It goes from 89,000 to several hundreds of thousands of people. If you are going to base who you are going to treat, treat sick people.

So if you have such a variability, then the number of doses you will need for sick people is going to be widely variable. Then you make the decision about is there going to be enough for health workers, and those formulas are easy because you know how many health workers you have. Are you going to have treatment available to incentivize health workers to come to work in the middle of a pandemic flu? That number is pretty easy to get.

The number that is the big variable is what is going to be the infection burden among people in this country. We have looked at those models. Obviously, it is greater than 2.3 million. Some say it is as high, in our own group, as 20 million treatment doses.

Mr. SHAYS. How long does a vaccine last?

Dr. FAUCI. Vaccine differs from therapy. Therapy shelf-life is about 5 years for Tamiflu. A vaccine, if you store it well it can last for a few years. The difficulty with vaccines is that the nature of

flu is that it keeps changing, so it is not a shelf-life issue. It is an effectiveness issue.

Mr. SHAYS. Thank you, Mr. Chairman.

Chairman TOM DAVIS. Mr. Ruppersberger.

Mr. RUPPERSBERGER. Let me have 5 minutes. There are three issues I would like to get into. No. 1 is planning. Congressman Shays got into it. I want to get into a little more specifics, the issue of injection devices, which I think are very relevant because it might be a way for us to use less vaccine and it might even be better. I think we need to look at that.

Also the issue of Tamiflu as it relates to children. Is there clinical testing going on right now? Let me get to that real quick. Where are we with Tamiflu and children?

Dr. FAUCI. Tamiflu is approved for children greater than 1-year-old for treatment and in individuals 13-plus years for prophylaxis. We are in the process of discussions of clinical trials to gather more information, particularly about the safety of Tamiflu in children 2 years of age and younger.

Mr. RUPPERSBERGER. I also understand that you are having problems with the industry as it relates to Tamiflu; that you are not getting the support that you need. Is that still the case?

Dr. FAUCI. I would say more that we are in active discussions trying to get that.

Mr. RUPPERSBERGER. I think that is really something that we need to deal with from an adversary point of view. If you want to lay it out now, I think we should discuss it because if industry is not cooperating, then we are putting everyone at risk, including the children. Where are we with respect to that issue, other than just saying "discussions?"

Dr. FAUCI. We are just in discussions, sir. I am not trying to evade the question. I checked with my staff yesterday and they said we are in active discussions about how we are going to get that information.

Mr. RUPPERSBERGER. It seems to me it should be aggressive discussions.

Dr. FAUCI. We, the NIH, are in an aggressive discussions.

Mr. RUPPERSBERGER. OK. Let me get to planning. In August, the administration released a draft, you probably have it there, you talked about your being before the Commerce Committee or whatever, saying you will have the draft this summer. You just testified to that.

Now, there were key elements in the first draft that were not addressed. I think we can all say that a key element of preparing for a flu pandemic is having a plan. Would you agree with that?

Dr. FAUCI. Absolutely.

Mr. RUPPERSBERGER. OK. Now, if that is the case, the areas that we are missing were undecided questions including how vaccines will be paid for and distributed; second, how scarce supplies of vaccines and drugs will be prioritized; and three, what messages will be communicated to the public in different stages of the pandemic.

Will they be addressed in the plan that you are coming up with this summer, those three elements?

Dr. GELLIN. Yes, to all.

Mr. RUPPERSBERGER. OK. I want to ask this question, too. I do not want to embarrass you because we want to move forward, but it seems to me that why don't we have a plan now? Canada finalized their plan in 2004. The United Kingdom finalized their plan in March 2005. Why is it taking us so long to get from the draft stage to the final plan?

Dr. GELLIN. We put out a draft last year and we left those areas open honestly to engage public discussion. We are disappointed with the lack of public input. We received few more than 50 comments to the plan that was posted in a 60-day period, because we thought that these areas, particularly the priority groups, were so important because as a pandemic could likely affect everybody in America, let alone everybody around the world, that we wanted to hear what people had to say and what the stakeholders had to say.

When we did not get much from that, we set up a process through the National Vaccine Advisory Committee and the Advisory Committee on Immunization Practices to begin to process that. There is a discussion this afternoon in Atlanta about that, and there is a joint meeting which I believe is the first joint meeting ever of these two Federal advisory committees in mid-July to come up with these recommendations to provide the Secretary.

Mr. RUPPERSBERGER. When you are talking about the health, safety and welfare of people, and then the media picks up on something, a lot of times the issue gets larger than maybe it is. But we cannot take any risks. I mean, we cannot take it for granted that there is not going to be a problem. I really think that it is important for the mindset of the industry, which is part of you all, to really start prioritizing and really do things quickly, and then communicate that to the public.

I can understand your answer about getting people to testify and doing it right, but as it relates to what is happening with flu, and now we hear about the bird issue, and that we really do not know what to do until it happens, are we ready to go, do we have the instrumentalities necessary.

With that, I want to get into injection devices. We talk a lot here about how much inventory we are going to have as far as the vaccine, but where are we with respect to injection devices? First thing, how many injection devices will be necessary to provide for the pandemic flu vaccine for the U.S. population? Can you answer that, anybody?

Dr. GELLIN. If it is the entire population, and we believe that there is going to be a requirement for possibly two doses, that number would be 600 million.

Mr. RUPPERSBERGER. Do you have a plan you can provide this committee on what these devices would be like? Do we have the technology necessary to make sure that they will do the job? Are we ahead of the curve as it relates to the rest of the world, as it relates to injection devices? And finally, do they work? Is it going to make it more efficient and using less of the flu vaccine if we use these devices instead of the needles that we use now?

Mr. SHAYS [presiding]. That will have to be the last question answered.

Dr. GELLIN. OK. There are several questions in there. Let me get to what I believe is the most interesting part of what you ask, and I may ask Dr. Fauci to back me up on that.

There is a global capacity for vaccine production of about 300 million doses of the trivalent vaccine. If you are going to make a single strain vaccine, so instead of three strains, a single strain, that could give you globally in a year maybe 900 million doses. That is the global industrial capacity.

Therefore, some of these devices that I think you are getting to might allow us to actually use less antigen per dose, and effectively stretch that global supply.

Dr. Fauci may want to get into some of this. The conversations they are having with the companies now to do those studies. There was one report in the New England Journal of Medicine last year which are promising, but we need to make sure these things work and provide the immune response that they need to.

Dr. FAUCI. We are actually in discussions about doing trials with different approaches, interdermal versus inter-muscular. Inter-muscular is simple needle-use. Injected interdemal, you can make it much more consistent if you have a needle.

Of course, it is not very difficult, but it requires some training to get the injection into the skin, which is what we called intra-dermal. That requires a different kind of an approach. We are in negotiations about doing a trial comparing one to the other. That does not address directly the question of how many of these devices are going to be available. It is more the proof of concept of whether or not you can use them.

Mr. SHAYS. Thank you.

The gentleman is right. Five minutes is not much time, but he had 7 minutes.

Mr. RUPPERSBERGER. Mr. Chairman, could I just ask for the record, not a question, but put a question for the record?

Mr. SHAYS. Sure.

Mr. RUPPERSBERGER. Do you think that the intra-dermal delivery of influenza vaccine has the potential to improve our preparedness for a flu pandemic?

Mr. SHAYS. And right after we find the answer to that question, we will throw it out, and before you leave we would like you to answer that question.

Mr. Dent.

Mr. DENT. Thank you, Mr. Chairman.

Good morning. I represent an area very close by, the Aventis plant up in Swiftwater, PA, and of course the flu issue is a big deal where I live, as it was in many communities. It caused me to think quite a bit about what lessons have we learned from this past season's flu vaccine shortage as far as distribution, prioritization and communication between State and local health officials, and what can we do to be better prepared for when an actual pandemic occurs, not just one that is naturally occurring, whether it be a flu, but perhaps some genetically engineered pathogen that could be injected by some non-state actor, from a homeland security standpoint. Can you just tell us the lessons that you have learned?

Dr. LEDUC. Thank you very much for that question, sir. Clearly, the challenges that we faced with the influenza vaccine availability

last year brought home several lessons, one of which is the critical importance of communication and active partnership with State and local health departments and partners as the situation evolves.

Another lesson is the real need for real-time communications on what is going on. Concurrently with that, a need for real flexibility because these issues we really do not have control over a lot of the situations that we are faced with. In that regard, we also learned that it is important to have plans in place up front that look at a variety of potential outcomes, especially with regard to delivery of flu vaccine in this particular case.

The other issue that we learned was that if we try to use a non-licensed product under an investigation of new drug application, that becomes very problematic. It is difficult to implement those.

Finally, I think the other lesson we learned is that it is very, very difficult to get the public to accept influenza vaccine beyond December of the calendar year.

Dr. FAUCI. There is another issue also, I just might add to that. It has to do with a question that I answered in response to Mr. Cummings' question. That is the vaccine enterprise and how fragile it is. What we do need is American companies making vaccine on American soil. We have foreign countries making it in Swiftwater. We have American companies making it in Liverpool. What we need is to have a greater commitment on the part of our own industrial partners here in the United States so that we can have a steady flow, and understanding of that each year.

Mr. DENT. What was your understanding as to why the vaccine flu was not being produced up in Swiftwater where they have the capacity to do so?

Dr. FAUCI. No, no, Swiftwater is doing a terrific job. They were our sole source this past year.

Mr. DENT. Correct.

Dr. FAUCI. No, the point I'm making is that we need to incentivize more companies to get involved in influenza vaccine manufacturing and production. That is what we really need.

Mr. DENT. How would you incentivize those companies?

Dr. FAUCI. Well, we have discussed again before this committee and other committees a number of things. There are several issues that have to do with financial incentives, and even stabilizing the influenza market, as it were. The CDC and the department has been trying over the past couple of years to get a greater number of people each year to routinely get vaccinated. We used to do 50 million or 60 million. We got it up to 80 million. We tried to get it to 100 million last year. We in fact probably need to go up to 150 million to 180 million.

Once we do that, then you have a stable pool of people who will be getting vaccinated, which makes it much more attractive to industry to get involved in a stable market, as opposed to a market where they do not know from 1 year to another whether they are going to have to throw away 10 million doses.

There are other incentives regarding liabilities and things like that we have spoken about in the past.

Mr. DENT. Thank you. No further questions.

Mr. SHAYS. Thank you.

Mrs. Maloney.

Mrs. MALONEY. You are the guys trying to help us solve this problem. I represented a city that really was in crisis when we did not have the vaccines. It was really terrible. We want to prevent that.

I think, Dr. Fauci, you hit it on the head when you said we have to produce it right here in the United States. One of the problems is we had to fly over to England. Then there were these questions about their standards, are they the same as ours, and all other kinds of things.

I guess we need to figure out how to handle this better. I guess I just want to hear any other ideas about how we can stockpile it here in the United States, it you cannot manufacture it, and then at least have the stockpile here. And do we have the budget in place to make these purchases?

One of the problems we had in the last crisis is that we could not buy it or we did not have the money to buy it, and there were all kinds of problems about making sure that when we were buying it overseas, it did meet the health standards of the United States, and how can we plan that better? Obviously, it would be better to manufacture it in the United States, but if we are not manufacturing it in the United States, how can we guarantee that we are going to have several people manufacturing it so that if one person has a problem in maintaining certain standards, there is another place we can go to.

I guess an important question is the budgeting. Do we have the budget to buy a stockpile and to put in place the planning for it.

I would like to start with Dr. Fauci and anyone else who would like to answer.

Dr. FAUCI. Thank you, Mrs. Maloney. That is a lot of questions there. Let me just take one of them to answer because it relates to what I just mentioned a moment ago, is how are we going to get these companies involved. That relates to the incentives that we need. We need a stable pool of people. We need protections against the liabilities that they face. We may even need things like tax incentives to build plants in the United States.

The issue of stockpiling, I will make a quick comment then I am sure that Dr. LeDuc can comment on that since the CDC is involved in small stockpiling issue each year.

Unlike other pharmaceuticals, it is very difficult to long-term stockpile influenza vaccine because even in a non-pandemic situation, it changes a bit from year to year, so almost invariably we have to deal with a small, sometimes moderate modification of the vaccine from year to year. So stockpiling for influenza just does not work in the big picture. You need a little stockpile the way the CDC has for the emergency situations, but a broader stockpile is just not tenable when you are dealing with a changing virus from year to year.

Dr. LEDUC. I would just agree with those comments. Stockpiling is not the solution to this particular problem for influenza. I think, as Dr. Fauci and Dr. Gellin have both said, the real issue is the fragility of our vaccine enterprise, and we really need to address that.

Dr. GELLIN. If I could comment, I think it is important to look at some of the changes in the marketplace. In 1990, as a Nation,

we used less than 30 million doses of influenza vaccine. That has been ratcheted up over time and there are a variety of reasons why that has been the case, but as a Nation, we have never used more than 83 million doses, while the CDC recommends that more than twice that many people receive an annual flu shot for their own personal health benefits.

Nevertheless, those numbers have increased dramatically. At the same time, I do not have the pricing information, the price has gone up; the reimbursement rates by CMS have gone up. It has become a more interesting marketplace for many manufacturers. We have seen this, and I think maybe it was last year that provided an opportunity for many more manufacturers to come and discuss with us. Dr. Fauci mentioned NIH working with GSK to produce some of the data, so they have brought their license application.

So I am hopeful that we will have more manufacturers to the marketplace in the near future.

Mrs. MALONEY. My time is almost up. I just would like to throw out, obviously we do not have time to get manufacturing going in our own country, so what are we going to do for next year? Last time, we only had one manufacturer, as I recall, that we were working with in England, and they were not up to our standards.

Are we contracting now with certain manufacturers in other countries for just this coming year? This is a long-term problem. We hear you and we are going to try to do something about it, but this flu season will be coming quickly and we do not have time to adjust in the United States. We are going to be dependent on foreign importation again, and how are we planning on that?

Dr. FAUCI. We have Sanofi-Pasteur standard, which was successful interaction with the last year. Chiron is getting back. It is a bit unclear exactly how many doses they are going to be able to give us, but there is a range of doses. We have been working with GlaxoSmithKline from the previous year about trying to get them in the market for X amount of doses, not exactly certain. So we now have at least three companies, in addition to MedImmune with their FluMist. So it is not just the single company for this coming year.

Mrs. MALONEY. Thank you. My time is up.

Mr. SHAYS. I thank the gentlelady.

We will turn now to the former chairman of this committee, Dan Burton.

Mr. BURTON. It is nice seeing you gentlemen again.

First of all, I want to congratulate you on addressing this issue. I think it is very important. I think we are all concerned about a major flu epidemic that might be started by radicals to try to destroy this country, or at least a part of it.

The question I would like to ask you deals with another subject. I know that you are aware that for about 4 or 5 years we held hearings when I was chairman of this committee on the mercury in the vaccines. I am very much in favor of the vaccine programs. I think they have given us the highest quality of life in the history of mankind. But we have gone from 1 in 10,000 children who are autistic, and I know there are questions about how you define somebody that is autistic and they split hairs on this, but we are now, according to CDC, at 1 out of 166 children that are autistic.

We had scientists and doctors before the committee when I was Chair that told us that there was no doubt in their minds, and these are not just fly by-night doctors and scientists, these are people from all over the world that believe that one of the major contributing factors of the autism and the epidemic of autism was the mercury in the vaccines.

Recently, Robert F. Kennedy, Jr., wrote an article which talks about meetings that took place in secret with our health agencies and some of the pharmaceutical companies. I will be happy to get you a copy of that. Have you seen that article? Do you know what I am talking about?

So there is a great deal of concern among people in this country about the mercury in the vaccines and the effect of that and what it is going to do to people long term, especially the kids who are going to live a long life and many of whom will be disabled because of the autism or neurological disorders.

But we are here today to talk about the flu vaccine. Every Member of Congress that I know of that is concerned about flu. At my age, we get a flu vaccine shot. I have gotten mine this year, even though I knew there was mercury in it. We still have thimerasol in most of the adult vaccines. Many of the scientists that came before this committee told us that not only did the mercury in the vaccines contribute to neurological disorders in children, but they believed it also had an adverse impact on older folks and could be a contributing factor in neurological problems such as Alzheimer's disease.

So I would just like to ask you, why don't we get the mercury out of all vaccines? It is not necessary. I know that they use because they use it in 10- or 20-shot vials for production purposes, but we could go to single-shot vials and eliminate that. I would like to know what our health agencies are doing about getting mercury, which is a very toxic substance, out of all vaccines.

In my district, we had a small breakage of a container that contained mercury. It was not much more than what would fill this cup. They evacuated two square blocks of people and brought in the fire department people to clean it up in uniforms that looked like they were from outer space. It was because mercury is so toxic.

Here in Washington, DC, they spilled some mercury in a high school laboratory and they burned all the children's shoes and clothes and everything else and got everybody out of the school while they cleaned up the mercury in that room.

So we know mercury is one of the most toxic substances in the world. It makes no sense to me to continue to have it in our vaccines. There is a growing body of evidence and scientists that believe that the mercury in the vaccines contributes to these neurological disorders in children and adults, and I would like for you to tell me today you are going to get it out of all vaccines. So, can you give me an answer, gentlemen?

Dr. LEDUC. Bruce might have more information, but you are right, sir. The single-dose vaccines for pediatrics, for I think all childhood vaccines, are free of mercury.

Mr. BURTON. There are three that still have mercury in them, three children's vaccines still have mercury.

Dr. LEDUC. I stand corrected then. I know at least the material that we have purchased for the stockpile for influenza is free of thimerasol.

The multi-dose vials, you are correct, continue to have a trace amount of thimerasol as a preservative in it. I do not have an answer as to how industry is going to work through that. Perhaps my colleagues do.

Dr. FAUCI. Certainly the ultimate goal is just what you are saying, Mr. Burton, is to get it out of all of the vaccines. The difficulty we are facing with influenza is the double problematic issue of trying to rev up and make it in as efficient a manner as possible, which really requires multi-dose right now. If to get it in a single dose, it would really be very difficult to meet the goal. That is not an excuse for forgetting about the issue of trying to get a thimerasol-free vaccine ultimately, which is what we are ultimately trying to do. But, unfortunately, it is not going to be for this year's cycle.

Mr. BURTON. If the Chair would bear with me for one more real brief comment. Dr. Fauci, I have high regard for all of you. I know that may seem insincere after all the hearings we have had, but I really do have high regard for all of you and our health agencies. I think you are doing the Lord's work by trying to protect this country. But we have been talking about getting mercury out of vaccines for at least 10 years, and it seems to me that the health agencies could put pressure on the producers to come up with an alternative to what we are using to make sure these vaccines are safe in multi-shot vials. Either that, or going to a production system that will create single-shot vials. And if we did that 5 years ago, 4 years ago, we wouldn't be talking about, oh, we can't do it right now on the flu vaccine.

So I really hope and I pray for the health of these people that are having these neurological problems—and the ones who will have them in the future—that we get on with the program and get mercury out of all vaccines as quickly as possible.

Thank you, Mr. Chairman.

Mr. SHAYS. I thank the gentleman.

Ambassador Watson.

Ms. WATSON. I want to thank the Chair and also the panelists for coming here, talking about influenza and our preparation. What I noticed last year is that we were scrambling around, and since Chiron admitted that its supply was contaminated, that put us in a very bad position and we saw people who really needed to get their shots, not being able to access the shots, and had to wait in long lines for hours, particularly our seniors.

So my question for Dr. Bruce Gellin is how are we planning if we run into this situation again—and I have been listening very intently. It seems like the supply is limited and we can't keep a supply over a period of time, and we seem not to have been able to buildup the capability to produce the solutions here for the shots. So what are we doing? How are we planning to take care of those in need? Who goes to the top of the list; where do they go; and what are our plans if this occurs again? That is question No. 1.

Dr. GELLIN. You ask all the relevant questions, the same questions my mother asked me when she called me from a grocery store

in Central Connecticut, asking how long the line was going to be. As we have highlighted, this is clearly a fragile business, and the disappointment we had last year when we lost half of our supply forced us to redistribute it.

I think the good news in that story was when we look back over the past year, we found that we actually did a pretty good job of getting it to high-risk people, and the messages of if you are at lower risk, step aside. I think there were some adjustments made to allow that to happen. Clearly, a large part of this, as you mention, is about communication, so should there be such an issue, it is very clear who is prioritized and the need to better communicate with both the health care community and the public health community about the distribution.

So I think that the lesson last year has put that part of the operation—which is largely the CDC—in place. At the same time, we have regular discussions with the manufacturers along the line so we can keep track of where they are in their anticipated supply over the year, and have mapped out just a few scenarios about how we would adjust things and how priority groups might be determined based on those supply situations.

Ms. WATSON. I was quite amazed last year that we didn't have a plan in place. What is further amazing me is the reasons why—and I think you were addressing those when I walked into the hearing—we have not developed the capability in this country, why we have not, decades ago, done the research to test the flu vaccines, and why we cannot manufacture. I understand that it is Canada and Great Britain that do the majority. Correct me if I am wrong. But we certainly have the ability to do that.

Is it a misplaced priority? Are we looking at other issues, rather than the protection of our people? Flu can kill, and it kills tens of thousand annually. And I don't know why we are not on top of it. Can someone enlighten me? What did I miss?

Dr. GELLIN. I can't speak to the history, but I can speak to the present. I believe that, in point of fact, the largest single manufacturer of influenza vaccine in the world is in Pennsylvania. There are maybe a dozen or so companies. We have one, Sanofi Pasteur, which is based in Pennsylvania, that I believe produces the single most influenza vaccine in one facility.

Ms. WATSON. For our country or others?

Dr. GELLIN. For our country.

Ms. WATSON. Well, what is the problem, why do we run short?

Dr. GELLIN. Well, we have more needs than that one manufacturer can make, which gets me to where we are now and what we are doing ahead. And I think it was the attention being paid to pandemic influenza, or some strategic investments, and Dr. LeDuc was mentioning about surge capacity. We have done a few things to shore up our supply, particularly with pandemic in mind. We have made sure that, in this case, Sanofi, has all the eggs that they need 24 hours a day to make as much vaccine as they can in a year. That was not a system they had in place beforehand. It is a seasonal disease and it is a seasonal vaccine, and we filled in that. So should they need, on any day of the year, to make vaccine at full capacity, they now have the eggs in place to do that.

But, more importantly, the next step is trying to think about the kinds of capacity and the kinds of production technologies that may improve where we are. Eggs have served us well, but they have some limitations, and we have put significant funds to try to accelerate the development of new technologies that can allow what we described as surge capacity and more vaccine to be produced.

And, finally, to that point, in addition to developing these vaccines, accelerating the development, getting them licensed, part of the criteria to this funding stream is to develop facilities so that ultimately these new vaccines will be produced in the United States.

Ms. WATSON. OK, I am sorry, I am out of time. I was just going to join with my friend, Congressman Dan Burton, on the mercury issue and the slow movement that has taken place slowly in trying to improve.

So there are other questions, too, but I know I am out of time, Mr. Chairman.

Mr. SHAYS. Thank you.

Ms. WATSON. Thank you for the time.

Mr. SHAYS. We have another that is a rather large panel, so we will get to that and just thank all of our witnesses. We will be following up with some questions. Mr. Burton may have some; I know the committee does. Ambassador Watson may as well, and the ranking member and others may. So thank you all very much.

We will announce our second panel. It is Dr. Crosse, Director of Health Care Issues, U.S. Government Accountability Office; Ms. Selecky, Washington State Secretary of Health, testifying on behalf of the Association of State and Territorial Health Officials; Dr. Hearne, executive director, Trust for America's Health; Dr. John Milligan, executive vice president and chief financial officer, Gilead Sciences, Inc.; and Mr. Abercrombie, president and chief executive officer, Hoffman-La Roche, Inc., accompanied by Dr. Dominick Iacuzio, medical director, Roche Laboratories.

We have enough seats for everyone there? Stay standing, if you would, because we are going to swear you in.

[Witnesses sworn.]

Mr. SHAYS. Note for the record our witnesses have responded in the affirmative.

And we will start with you, Dr. Crosse, and we will just go right up.

Dr. CROSSE. Thank you.

Mr. SHAYS. Five minutes is the time allotted. Obviously, if you go over a minute or two, we can live with that. But we have a large panel and a busy schedule today. Thank you.

Dr. Crosse.

STATEMENTS OF DR. MARCIA CROSSE, DIRECTOR, HEALTH CARE ISSUES, U.S. GOVERNMENT ACCOUNTABILITY OFFICE; MARY C. SELECKY, WASHINGTON STATE SECRETARY OF HEALTH, TESTIFYING ON BEHALF OF THE ASSOCIATION OF STATE AND TERRITORIAL HEALTH OFFICIALS; DR. SHELLEY A. HEARNE, EXECUTIVE DIRECTOR, TRUST FOR AMERICA'S HEALTH; DR. JOHN F. MILLIGAN, EXECUTIVE VICE PRESIDENT AND CHIEF FINANCIAL OFFICER, GILEAD SCIENCES, INC.; AND GEORGE B. ABERCROMBIE, PRESIDENT AND CHIEF EXECUTIVE OFFICER, HOFFMAN-LA ROCHE, INC., ACCOMPANIED BY DR. DOMINICK IACUZIO, MEDICAL DIRECTOR, ROCHE LABORATORIES, INC.

STATEMENT OF DR. MARCIA CROSSE

Dr. CROSSE. Thank you. I am pleased to be here today as you discuss issues regarding our preparedness to respond to an influenza pandemic. Shortages of influenza vaccine in the 2004–2005 influenza season, as well as mounting concern about avian influenza activity in Asia, have raised concerns about the Nation's preparedness to deal with a pandemic.

As we have heard, given the global nature of disease, a pandemic that begins abroad could quickly spread to this country.

You asked us to provide our perspective on the Nation's preparedness for responding to an influenza pandemic, including lessons learned from the previous influenza season, that would be applicable for pandemic preparedness.

Although an influenza pandemic will differ from a routine influenza season, experience during the 2004–2005 shortage illustrates the importance of developing a workable distribution plan, identifying priority groups in local populations, and developing plans for mass vaccinations in advance.

The Nation faces multiple challenges to prepare for and respond to an influenza pandemic. Key questions remain about the Federal role in purchasing and distributing vaccines during a pandemic. HHS's current draft pandemic preparedness plan does not establish the actions the Federal Government would take to purchase or distribute vaccine during an influenza pandemic, and leaves it up to States to select among three options: public sector purchase of all pandemic influenza vaccine; a mixed public-private system, where public sector supply may be targeted to specific priority groups; or maintenance of the current, largely private, system.

However, if States are to purchase vaccine, they may need to undertake efforts in advance to establish the necessary funding sources, authority, or processes. For example, during this past winter, the State of Minnesota tried to sell some of its vaccine to other States that needed additional vaccine for their high-risk populations. But some States lacked the funding or authority under State law to purchase the vaccine when Minnesota offered it.

HHS's draft pandemic plan indicates that, as information about virus severity becomes available, recommendations on priority groups for early vaccination will be developed at the national level. However, during the past vaccination season, in some places there was not enough vaccine to cover everyone in the priority groups, so States set their own priorities. Maine, for example, initially ex-

cluded healthcare workers because State officials estimated that there was not enough vaccine to cover everyone in the nationally designated groups.

In addition, clear communication will be a big challenge. State health officials reported this past winter that mixed messages created confusion. For example, when CDC advised those persons aged 65 and over to get vaccinated, and some States, including California, advised those persons aged 50 and over to get vaccinated.

Further, some individuals found themselves in a communication loop that provided no answers on where to be vaccinated. CDC advised people to contact their local public health department. However, some public health departments told callers to contact their physician. But when they called their physician, they were told to call their public health department. This lack of a reliable source of information led to confusion and much frustration.

Further challenges include ensuring an adequate and timely supply of influenza vaccine and antiviral drugs, which can help prevent or mitigate the number of influenza-related deaths. As we learned this past season, and as we have heard repeatedly today, the vaccine supply is fragile; it takes many months to produce vaccine; and problems with even a single manufacturer can result in vaccine shortages. Particularly given the length of time needed to produce vaccines, influenza vaccine may be unavailable, in short supply, or delayed, and might not be widely available during the initial stages of a pandemic.

Further, our current stockpile of antiviral drugs is insufficient to meet the likely demand in a pandemic. As was discussed earlier, HHS is working to expand vaccine production capacity and to stockpile vaccine and antiviral drugs, but it will be years before these preparations are in place.

Finally, the lack of sufficient hospital and healthcare work force capacity to respond to an infectious disease outbreak may also affect response efforts during an influenza pandemic. Public health officials we spoke with said that, at a minimum, a large-scale outbreak could strain the available capacity of hospitals by requiring entire hospital sections, along with their staff, to be used as isolation facilities.

In summary, important challenges remain in the Nation's preparedness and response should an influenza pandemic occur in the United States. As we learned in the 2004–2005 influenza season, when vaccine supply is limited, planning and effective communication are critical to ensure timely delivery of vaccine to those who need it. HHS's current draft plan lacks some key information for planning our Nation's response to a pandemic.

It is important for the Federal Government and the State to work through critical issues, such as how vaccine will be purchased, distributed, and administered; which population groups are likely to have priority for vaccination; what communication strategies are most effective; and how to address issues related to vaccine and antiviral supply, and hospital and work force capacity before we are in a time of crisis.

Until key Federal decisions are made, public health officials at all levels may find it difficult to plan for an influenza pandemic, and the timeliness and adequacy of response efforts may be compromised.

Mr. Chairman, this concludes my prepared statement.

[The prepared statement of Dr. Crosse follows:]

United States Government Accountability Office

GAO

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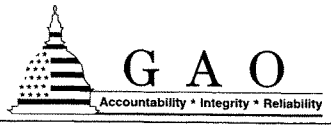
INFLUENZA PANDEMIC

Challenges in Preparedness and Response

Statement of Marcia Crosse
Director, Health Care



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Highlights

Highlights of GAO-05-863T, a testimony before the Committee on Government Reform, House of Representatives

INFLUENZA PANDEMIC

Challenges in Preparedness and Response

Why GAO Did This Study

Shortages of influenza vaccine in the 2004–05 and previous influenza seasons and mounting concern about recent avian influenza activity in Asia have raised concern about the nation's preparedness to deal with a worldwide influenza epidemic, or influenza pandemic. Although the extent of such a pandemic cannot be predicted, according to the Centers for Disease Control and Prevention (CDC), an agency within the Department of Health and Human Services (HHS), it has been estimated that in the absence of any control measures such as vaccination or antiviral drugs, a "medium-level" influenza pandemic could kill up to 207,000 people in the United States, affect from 15 to 35 percent of the U.S. population, and generate associated costs ranging from $71 billion to $167 billion in the United States.

GAO was asked to discuss the challenges the nation faces in responding to the threat of an influenza pandemic, including the lessons learned from previous annual influenza seasons that can be applied to its preparedness and overall ability to respond to a pandemic. This testimony is based on GAO reports and testimony issued since 2000 on influenza vaccine supply, pandemic planning, emergency preparedness, and emerging infectious diseases and on current work examining the influenza vaccine shortage in the United States for the 2004–05 influenza season.

www.gao.gov/cgi-bin/getrpt?GAO-05-863T.

To view the full product, including the scope and methodology, click on the link above. For more information, contact Marcia Crosse at (202) 512-7119.

What GAO Found

The nation faces multiple challenges to prepare for and respond to an influenza pandemic. First, key questions about the federal role in purchasing and distributing vaccines during a pandemic remain, and clear guidance on potential priority groups is lacking in HHS's current draft of its pandemic preparedness plan. For example, the draft plan does not establish the actions the federal government would take to purchase or distribute vaccine during an influenza pandemic. In addition, as was highlighted in the nation's recent experience responding to the unexpected influenza vaccine shortage for the 2004–05 influenza season, clear communication of the nation's response plan will be a major challenge. During the 2004–05 influenza season, state health officials reported that mixed messages created confusion. For example, CDC advised vaccination for persons aged 65 and older, and at the same time a state advised vaccination for persons aged 50 and older. Further challenges include ensuring an adequate and timely supply of influenza vaccine and antiviral drugs, which can help prevent or mitigate the number of influenza-related deaths. Particularly given the length of time needed to produce vaccines, influenza vaccine may be unavailable or in short supply and might not be widely available during the initial states of a pandemic. Finally, the lack of sufficient hospital and health care workforce capacity to respond to an infectious disease outbreak may also affect response efforts during an influenza pandemic. Public health officials we spoke with said that a large-scale outbreak, such as an influenza pandemic, could strain the available capacity of hospitals by requiring entire hospital sections, along with their staff, to be used as isolation facilities.

Mr. Chairman and Members of the Committee:

I am pleased to be here today as you discuss the nation's preparedness to respond to a worldwide influenza epidemic—known as a pandemic.[1] Shortages of influenza vaccine in the 2004–05 and previous annual influenza seasons, as well as mounting concern about recent avian influenza activity in Asia, have raised concern about the nation's preparedness to deal with a pandemic. Pandemic influenza, which arises periodically but unpredictably from a major genetic change in the influenza virus, can lead to worldwide disease and death.[2] Although the extent of the next pandemic cannot be predicted, modeling studies suggest that its effect in the United States could be severe. According to the Centers for Disease Control and Prevention (CDC), it has been estimated that in the absence of any control measures such as vaccination and drugs, a "medium-level" influenza pandemic in the United States could kill 89,000 to 207,000 people, affect from 15 to 35 percent of the U.S. population, and generate associated costs ranging from $71 billion to $167 billion. In the event of a pandemic, the nation will likely experience a vaccine shortage. The nation's experience responding to the unexpected shortage of annual influenza vaccine during the 2004–05 influenza season—in which public health officials sought to match available vaccine supply with demand—underscores the challenges that federal, state, and local entities would need to meet in the event of a pandemic. In addition, our recent work has highlighted other challenges in responding to pandemic influenza.

You asked us to provide our perspective on the nation's preparedness for responding to an influenza pandemic, including the lessons learned from previous annual influenza seasons that would be applicable to pandemic preparedness. In this testimony, I will discuss challenges we identified related to (1) planning for the purchase and distribution of influenza vaccine, including defining priority groups to be vaccinated; (2) communicating information about the situation and the response plan clearly and effectively among health officials, providers, and the public;

[1]An influenza pandemic is defined by the emergence of a novel influenza virus, to which much or all of the population is susceptible, that is readily transmitted person to person, and causes outbreaks in multiple countries.

[2]Influenza pandemics can have successive "waves" of disease and last for up to 3 years. Three pandemics occurred in the 20th century: the "Spanish influenza" of 1918, which killed about 500,000 people in the United States; the "Asian influenza" of 1957, which killed about 70,000 people in the United States; and the "Hong Kong influenza" of 1968, which killed about 34,000 people in the United States.

(3) ensuring an adequate supply of vaccine and antiviral drugs; and
(4) addressing hospital and workforce capacity to respond to large-scale outbreaks of infectious disease, including pandemic influenza.

My testimony today is based on reports and testimony on influenza vaccine supply, pandemic planning, emergency preparedness, and emerging infectious diseases that we have issued since October 2000[3] and on a review in progress for this committee on actions taken and lessons learned at federal, state, and local levels to ensure that high-risk individuals had access to vaccine during the 2004–05 influenza vaccine shortage. Our prior work includes analysis of information provided by and interviews with officials in the Department of Health and Human Services (HHS), specifically from CDC, the Food and Drug Administration (FDA), and the National Vaccine Program Office. We also interviewed public health department officials, vaccine manufacturers, and vaccine distributors; surveyed physician group practices; and reviewed HHS's August 2004 draft *Pandemic Influenza Preparedness and Response Plan*. Since March 2005 we have reviewed documents and interviewed officials from HHS, CDC, and the National Vaccine Program Office; national organizations, including the Association of State and Territorial Health Officials; organizations that conduct mass immunization clinics; a major vaccine manufacturer; and a large purchaser of influenza vaccine. We also conducted site visits at a judgmental sample of states and localities.[4] We conducted our work in accordance with generally accepted government auditing standards. CDC and the National Vaccine Program Office provided comments on the facts contained in this statement, and we made changes as appropriate.

In summary, the nation faces multiple challenges to prepare for and respond to an influenza pandemic. First, key questions remain about the federal role in purchasing and distributing vaccines during a pandemic, and clear guidance on potential priority groups is lacking in HHS's current draft of its pandemic preparedness plan. In addition, as highlighted by the nation's recent experience responding to the unexpected influenza vaccine

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

[4]The states included California, Florida, Maine, Minnesota, and Washington, and the localities included San Diego and San Francisco, California; Miami–Dade County, Florida; Portland, Maine; Stearns County, Minnesota; and Seattle–King County, Washington. We selected these states and localities on the basis of geography, population size, and state vaccination success rates.

shortage for the 2004–05 influenza season, clear communication of the nation's response plan will be a major challenge. Further challenges include ensuring an adequate and timely supply of influenza vaccine and antiviral drugs, which can help prevent or mitigate the number of influenza-related deaths. Finally, the lack of sufficient hospital and health care workforce capacity to respond to an infectious disease outbreak may also affect response efforts during an influenza pandemic.

Background

Influenza is more severe than some other viral respiratory infections, such as the common cold. Most people who contract influenza recover completely in 1 to 2 weeks, but some develop serious and potentially life-threatening medical complications, such as pneumonia. People aged 65 and older, people of any age with chronic medical conditions, children younger than 2 years, and pregnant women are generally more likely than others to develop severe complications from influenza.

Vaccination is the primary method for preventing influenza and its more severe complications. Produced in a complex process that involves growing viruses in millions of fertilized chicken eggs, influenza vaccine is administered annually to provide protection against particular influenza strains expected to be prevalent that year. Experience has shown that vaccine production generally takes 6 or more months after a virus strain has been identified; vaccines for certain influenza strains have been difficult to mass-produce. After vaccination, it takes about 2 weeks for the body to produce the antibodies that protect against infection. According to CDC recommendations, the optimal time for vaccination is October through November, because the annual influenza season typically does not peak until January or February. Thus, in most years vaccination in December or later can still be beneficial.

At present, two vaccine types are recommended for protection against influenza in the United States: an inactivated virus vaccine injected into muscle and a live virus vaccine administered as a nasal spray. The injectable vaccine—which represents the large majority of influenza vaccine administered in this country—can be used to immunize healthy individuals and those at highest risk for complications, including those with chronic illness and those aged 65 and older, but the nasal spray vaccine is currently approved for use only among healthy individuals aged 5 to 49 years who are not pregnant. Vaccine manufacture and purchase

take place largely within the private sector: for the 2004–05 influenza season, two companies (one producing the injectable vaccine and one producing the nasal spray) manufactured vaccine for the U.S. market.[5]

Although vaccination is the primary strategy for protecting individuals who are at greatest risk of serious complications and death from influenza, antiviral drugs can also contribute to the treatment and prevention of influenza. Four antiviral drugs have been approved for treatment. If taken within 2 days after symptoms begin, these drugs can reduce symptoms and make someone with influenza less contagious to others. Three of the four antiviral drugs are also approved for prevention; according to CDC, they are about 70 to 90 percent effective for preventing illness in healthy adults.

HHS has primary responsibility for coordinating the nation's response to public health emergencies. As part of its mission, the department has a role in the planning needed to prepare for and respond to an influenza pandemic. One action the department has taken is to develop a draft national pandemic influenza plan, titled *Pandemic Influenza Preparedness and Response Plan*, which was released in August 2004 for a 60-day comment period. Within HHS, CDC is the principal agency for protecting the nation's health and safety. CDC's activities include efforts to prevent and control diseases and to respond to public health emergencies. CDC and its Advisory Committee on Immunization Practices (ACIP) recommend which population groups should be targeted for vaccination each year and, when vaccine supply allows, recommends that any person who wishes to decrease his or her risk of influenza-like illness be vaccinated. FDA, another HHS agency, also plays a role in preparing for the annual influenza season and for a potential pandemic. FDA is responsible for ensuring that new vaccines and drugs are safe and effective. The agency also regulates and licenses vaccines and antiviral agents.[6]

HHS has limited authority to control vaccine production and distribution directly; influenza vaccine supply and marketing are largely in the hands of

[5]HHS also located and purchased about 1.5 million doses of vaccine from manufacturers not licensed in the United States. Although this vaccine could be made available to be administered under special protocols, according to HHS officials, none of the vaccine was used in the 2004–05 influenza season.

[6]In addition, FDA develops influenza reference strains and reagents and makes them available to manufacturers for vaccine development and evaluation.

the private sector.[7] Although the Public Health Service Act authorizes the Secretary of HHS to "take such action as may be appropriate" to respond to a public health emergency, as determined and declared by the Secretary, it is not clear whether or to what extent the Secretary could directly influence the manufacture or distribution of influenza vaccine to respond to an influenza pandemic.[8] The appropriateness of the Secretary's response would depend on the nature of the public health emergency, for example on the available evidence relating to a pandemic. According to a senior HHS official involved in HHS emergency preparedness activities, manufacturers of vaccine for the U.S. market have agreed in principle to switch to production of pandemic influenza vaccine should the need arise and proper compensation and indemnification be provided; therefore, he said, it would probably be unnecessary for the federal government to nationalize vaccine production, although the federal government has the legal authority to do so if circumstances warrant it.

For the 2004–05 influenza season, CDC estimated as late as September 2004 that about 100 million doses of vaccine would be available for the U.S. market.[9] CDC and ACIP recommended vaccination for about 185 million people, including roughly 85 million people at high risk for complications.[10] On October 5, 2004, however, one manufacturer announced that it could not provide its expected production of 46–48 million doses—roughly half of the U.S. supply of expected vaccine.[11]

[7]Under the Federal Food, Drug, and Cosmetic Act, FDA ensures compliance with good manufacturing practice. FDA has limited authority to prohibit 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.

[8]According to the act, to declare a public health emergency, the Secretary must determine that (1) a disease or disorder presents a public health emergency or (2) a public health emergency, including significant outbreaks of infectious disease or bioterrorist attacks, otherwise exists. Public Health Service Act § 319 (current version at 42 U.S.C. § 247d).

[9]See Centers for Disease Control and Prevention, "Supplemental Recommendations about Timing of Influenza Vaccination, 2004–05 Season," *Morbidity and Mortality Weekly Report*, vol. 53, no. 37 (2004): 878–879.

[10]Not everyone in target populations receives a vaccination each year. See Centers for Disease Control and Prevention, "Prevention and Control of Influenza Recommendations of the Advisory Committee on Immunization Practices (ACIP)," *Morbidity and Mortality Weekly Report*, vol. 53, no. RR-06 (2004): 1–40.

[11]The license for this manufacturer, with production facilities in Liverpool, England, was temporarily suspended by British regulatory authorities.

Because a large proportion of vaccine produced by the other major manufacturer of injectable vaccine had already been shipped before October 5, 2004, about 25 million doses of injectable vaccine for high-risk individuals and others, and about 1 million doses of the nasal spray vaccine for healthy people, were available after the announcement to be distributed to Americans who wanted an influenza vaccination.

Preparing for and responding to an influenza pandemic differ in several respects from preparing for and responding to a typical influenza season. For example, past influenza pandemics have affected healthy young adults who are not typically at high risk for complications associated with influenza, and a pandemic could result in an overwhelming burden of ill persons requiring hospitalization or outpatient medical care. In addition, the demand for vaccine may be greater in a pandemic.

Planning for Purchase and Distribution of Vaccine and Defining Priority Groups

Challenges remain in planning for purchase and distribution of vaccine and defining priority groups in the event of a pandemic. HHS has not finalized planning for an influenza pandemic, leaving unanswered questions about the nation's ability to prepare for and respond to such an outbreak. For the past 5 years, we have been urging HHS to complete its pandemic influenza plan. The document remains in draft form, although federal officials said in June 2005 that an update of the plan is being completed and is expected to be available in summer 2005. Key questions about the federal role in purchasing and distributing vaccines during a pandemic remain, and clear guidance on potential groups that would likely have priority for vaccination is lacking in the current draft plan.

One challenge is that the draft pandemic plan does not establish the actions the federal government would take to purchase or distribute vaccine during an influenza pandemic. Rather, it describes options for vaccine purchase and distribution, which include public-sector purchase 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. The draft plan does not specifically recommend any of these options. According to the draft plan, the federal government's role may change over the course of a pandemic, with greater federal involvement early, when vaccine is in short supply. Noting that several uncertainties make planning vaccination strategies difficult, the draft plan states that national, state, and local planning needs to address possible contingencies, so that appropriate strategies are in place for whichever situation arises.

If public-sector vaccine purchase is an option, establishing the funding sources, authority, or processes to do so quickly may be needed. During the 2004–05 shortage, some state health officials reported problems with states' ability, with regard to both funding and the administrative process, to purchase influenza vaccine. For example, during the effort to redistribute vaccine to locations of greatest need, the state of Minnesota tried to sell its available vaccine to other states seeking additional vaccine for their high-risk populations. According to federal and state health officials, however, certain states lacked the funding or authority under state law to purchase the vaccine when Minnesota offered it. In response to problems encountered during the 2004–05 shortage, the Association of Immunization Managers proposed in 2005 that federal funds be set aside for emergency purchase of vaccine by public health agencies and that cost not be a barrier in acquiring vaccine to distribute to the public.[12]

Although an influenza pandemic may differ from an annual influenza season, experience during the 2004–05 shortage illustrates the importance of having a distribution plan in place ahead of time to prevent delays when timing is critical:

- **Collaborating with stakeholders to create a workable distribution plan is time consuming.** After the October 5, 2004, announcement of the sharp reduction in influenza vaccine supply, CDC began working with the sole remaining manufacturer of injectable vaccine on plans to distribute this manufacturer's remaining supply to providers across the country. The plan had two phases and benefited from voluntary compliance by the manufacturer to share proprietary information to help identify geographic areas of greatest need for vaccine. The first phase, which began in October 2004, filled or partially filled orders from certain provider types, including state and local public health departments and long-term care facilities. The second phase, which began in November 2004, used a formula to apportion the remaining doses across the states according to each state's estimated percentage of the national unmet need. States could then allocate doses from their apportionment to providers and facilities, which would purchase the vaccine through a participating distributor. The state ordering process under the second phase continued through mid-January. Health officials in several states commented on the late availability of this vaccine; officials in one state, for example, remarked that the phase two vaccine was "too much, too late."

[12]The Association of Immunization Managers is an organization that represents 64 state, territorial, and urban-area immunization programs funded by CDC.

- **Identifying priority groups in local populations also takes time.** Federal, state, and local officials need to have information on the population of the priority groups and the locations where they can be vaccinated to know how, where, and to whom to distribute vaccine in the event of an influenza pandemic. During the 2004–05 influenza season, federal officials developed a distribution plan to allocate a limited amount of vaccine, but the states also had to determine how much vaccine was needed and where to distribute it within their own borders. For example, state health officials in Florida did not know exactly how many high-risk individuals needed vaccination, so they surveyed long-term care facilities and private providers to estimate the amount of vaccine needed to cover high-risk populations. It took nearly a month for state officials to compile the results of the surveys, to decide how many doses needed to be distributed to local areas, and to receive and ship vaccine to the counties.

- **Distributing the vaccine to a state or locality is not the same as administering the vaccine to an individual.** Once vaccine has been distributed to a state or local agency, individuals living in those areas still need to be vaccinated. Vaccinating a large number of people is challenging, particularly when demand exceeds available supply. For example, during the 2004–05 influenza season, many places giving vaccinations right after the shortage was announced were overwhelmed with individuals wanting to be vaccinated. Certain local public health departments in California, including the Santa Clara County Public Health Department, provided chairs and extra water for people waiting in long lines outdoors in warm weather. Fear of a more virulent pandemic influenza strain could exacerbate such scenarios. A number of states reported that they did not have the capacity to immunize large numbers of people and partnered with other organizations to increase their capacity. For example, in 2004–05, according to state health officials in Florida, county health departments, including those in Orange and Broward Counties, worked with a national home health organization to immunize high-risk individuals by holding mass immunization clinics and setting up clinics in providers' offices to help administer available vaccine quickly. Other locations, including the local health department in Portland, Maine, held lotteries for available vaccine; according to local health officials, however, administrative time was required to arrange and publicize the lottery.

HHS's draft pandemic plan does not define priority groups for vaccination, although the plan states that HHS is developing an initial list of suggested priority groups and soliciting public comment on the list. The draft plan instructs the states to define priority groups for early vaccination and indicates that as information about virus severity becomes available,

recommendations will be formulated at the national level. According to the plan, setting priorities will be iterative, tied to vaccine availability and the pandemic's progression. Without agreed-upon identification of potential priority groups in advance, however, problems can arise. During the 2004–05 season, for example, CDC and ACIP acted quickly on October 5, 2004, to narrow the priority groups for available vaccine, giving the narrowed groups equal importance.[13] In some places, however, there was not enough available vaccine to cover everyone in these narrowed priority groups, so states set their own priorities among these groups. Maine, for example, excluded health care workers from the state's early priority groups because state officials estimated that there was not enough vaccine to cover everyone in CDC and ACIP's priority groups.

Communicating Information about the Situation and Response Plan Clearly and Effectively

Another challenge in responding to a pandemic will be to clearly communicate information about the situation and the nation's response plans to public health officials, providers, and the public. Experience during the 2004–05 vaccine shortage illustrates the critical role communication plays when information about vaccine supply is unclear.[14]

- **Communicating a consistent message and clearly explaining any apparent inconsistencies.** In a pandemic, clear communication on who should be vaccinated will be important, particularly if the priority population differs from those targeted for annual influenza vaccination, or if the priority groups in one area of the country differ from those in others. During the 2004–05 influenza season, health officials in Minnesota reported that some confusion resulted when the state determined that

[13]On October 5, 2004, CDC, in coordination with ACIP, issued interim recommendations for influenza vaccination during the 2004–05 season that took precedence over earlier recommendations. The season's priority groups for vaccination with injectable influenza vaccine were considered to be of equal importance. They included all children aged 6–23 months, adults aged 65 years and older, persons aged 2–64 years with underlying chronic medical conditions, all women who would be pregnant during the influenza season, residents of nursing homes and long-term care facilities, children aged 6 months–18 years on chronic aspirin therapy, health care workers involved in direct patient care, and out-of-home caregivers and household contacts of children younger than 6 months. See Centers for Disease Control and Prevention, "Interim Influenza Vaccination Recommendations, 2004–05 Influenza Season," *Morbidity and Mortality Weekly Report*, vol. 53, no. 39 (2004): 923–924.

[14]According to CDC officials, as part of preparations for the 2005–06 influenza season, the agency is preparing communication strategies with appropriate messages to respond to the fluctuations in supply and demand anticipated throughout the season. CDC has developed the communication plan but has not released the plan, as it is in the clearance process.

vaccine was sufficient to meet demand among the state's narrower priority groups and made vaccine available to other groups, such as healthy individuals aged 50–64 years, earlier than recommended by CDC. Health officials in California reported a similar situation. State health officials pointed out that in mid-December, local radio stations in California were running two public service announcements—one from CDC advising those 65 and older to be vaccinated and one from the California Department of Health Services advising those 50 and older to be vaccinated. State officials emphasized that these mixed messages created confusion.

- **Communicating information from a primary source.** Having a primary and timely source of information will be important in a pandemic. In the 2004–05 influenza season, individuals seeking vaccine could have found themselves in a communication loop that provided no answers. For example, CDC advised people seeking influenza vaccine to contact their local public health department; in some cases however, individuals calling the local public health department would be told to call their primary care provider, and when they called their primary care provider, they would be told to call their local public health department. This lack of a reliable source of information led to confusion and possibly to high-risk individuals' giving up and not receiving the protection of an annual influenza vaccination.[15]

- **Recognizing that different communication mechanisms are important and require resources.** Another challenge in communicating plans in the event of a pandemic will be to ensure that the communication mechanisms used reach all affected populations. During the 2004–05 influenza season, public health officials reported the importance of different methods of communication. For example, officials from the Seattle–King County Public Health Department in Washington State reported that it was important to have a hotline as well as information posted on a Web site, because some seniors calling Seattle–King County's hotline reported that they did not have access to the Internet. According to state and local health officials, however, maintaining these communication mechanisms took time and strained personnel resources. In Minnesota, for example, to supplement state employees, the state health department

[15]According to data collected during December 1–11, 2004, on self-reported vaccination during September 1 through November 30, 2004, among adults in priority groups who had not yet received influenza vaccine, about 23 percent reported that they attempted to obtain vaccination but could not. See Centers for Disease Control and Prevention, "Estimated Influenza Vaccination Coverage among Adults and Children—United States, September 1–November 30, 2004," *Morbidity and Mortality Weekly Report*, vol. 53, no. 49 (2004): 1147–1150.

asked public health nursing students to volunteer to staff the state's influenza vaccine hotline.

- **Educating health care providers and the public about all available vaccines**. For the 2004–05 season, approximately 3 million doses of nasal spray vaccine were ultimately available for vaccinating healthy individuals aged 5–49 years who were not pregnant, including some individuals (such as health care workers in this age group and household contacts of children younger than 6 months) in the priority groups defined by CDC and ACIP, yet some of these individuals were reluctant to use this vaccine because they feared that the live virus in the nasal spray could be transmitted to others. State health officials in Maine, for example, reported that the state purchased about 1,500 doses of the nasal spray vaccine for their emergency medical service personnel and health care workers, yet administered only 500 doses.

Ensuring Supply of Influenza Vaccine and Antiviral Drugs

Challenges in ensuring an adequate and timely supply of influenza vaccine and antiviral drugs—which can help prevent or mitigate the number of influenza-related deaths until an pandemic influenza vaccine becomes available—may be exacerbated during an influenza pandemic. Particularly given the time needed to produce vaccines, influenza vaccine may be unavailable or in short supply and may not be widely available during the initial stages of a pandemic. According to CDC, maintaining an abundant annual influenza vaccine supply is critically important for protecting the public's health and improving our preparedness for an influenza pandemic. The shortages of influenza vaccine in 2004–05 and previous seasons have highlighted the fragility of the influenza vaccine market and the need for its expansion and stabilization.

In its budget request for fiscal year 2006, CDC reports that it plans to take steps to ensure an expanded influenza vaccine supply. The agency's fiscal year 2006 budget request includes $30 million for CDC to enter into guaranteed-purchase contracts with vaccine manufacturers to ensure the production of bulk monovalent influenza vaccine. If supplies fall short, this bulk product can be turned into a finished trivalent influenza vaccine product for annual distribution.[16] If supplies are sufficient, the bulk vaccine can be held until the following year's influenza season and developed into finished vaccines if the bulk products maintain their

[16]Monovalent influenza vaccine protects against a single strain of influenza; trivalent influenza vaccine protects against three strains of influenza.

potency and the circulating strains remain the same. According to CDC, this guarantee will help expand the influenza market by providing an incentive to manufacturers to expand capacity and possibly encourage additional manufacturers to enter the market. In addition, CDC's fiscal year 2006 budget request includes an increase of $20 million to support influenza vaccine purchase activities.[17]

In the event of a pandemic, before a vaccine is available or during a period of limited vaccine supply, use of antiviral drugs could have a significant effect. Antiviral drugs can be used against all strains of pandemic influenza and, because they can be manufactured and stored before they are needed, could be available both to prevent illness and, if administered within 48 hours after symptoms begin, to treat it. Like vaccine, antiviral drugs take several months to produce from raw materials, and according to one antiviral drug manufacturer, the lead time needed to scale up production capacity and build stockpiles may make it difficult to meet any large-scale, unanticipated demand immediately. HHS' National Vaccine Program Office also reported that in a pandemic, the manufacturing capacity and supply of antiviral drugs is likely to be less than the global demand. For these reasons, the National Vaccine Program Office reported that analysis is under way to determine optimal strategies for antiviral drug use when supplies are suboptimal; the office also noted that antiviral drugs have been included in the national stockpile. HHS has purchased more than 7 million doses of antiviral drugs for the national stockpile.

Nevertheless, this stockpile is limited, and it is unclear how much will be available in the event of a pandemic, given existing production capacity. Moreover, some influenza virus strains can become resistant to one or more of the four approved influenza antiviral drugs, and thus the drugs may not always work. For example, the avian influenza virus strain (H5N1) identified in human patients in Asia in 2004 and 2005 has been resistant to two of four existing antiviral drugs.

[17]The $20 million increase is for CDC's Immunization Grant Program that provides vaccines for children, adolescents, and adults who present primarily at local health departments but are not eligible for CDC's Vaccines for Children program.

Hospital and Workforce Capacity to Respond to Large-Scale Infectious Disease Outbreaks

The lack of sufficient hospital and workforce capacity is another challenge that may affect response efforts during an influenza pandemic. The lack of sufficient capacity could be more severe during an influenza pandemic compared with other natural disasters, such as a tornado or hurricane, or with an intentional release of a bioterrorist agent because it is likely that a pandemic would result in widespread and sustained effects. Public health officials we spoke with said that a large-scale outbreak, such as an influenza pandemic, could strain the available capacity of hospitals by requiring entire hospital sections, along with their staff, to be used as isolation facilities. In addition, most states lack surge capacity—the ability to respond to the large influx of patients that occurs during a public health emergency. For example, few states reported having the capacity to evaluate, diagnose, and treat 500 or more patients involved in a single incident. In addition, few states reported having the capacity to rapidly establish clinics to immunize or treat large numbers of patients. Moreover, shortages in the health care workforce could occur during an influenza pandemic because higher disease rates could result in high rates of absenteeism among workers who are likely to be at increased risk of exposure and illness or who may need to care for ill family members.

Concluding Observations

Important challenges remain in the nation's preparedness and response should an influenza pandemic occur in the United States. As we learned in the 2004–05 influenza season, when vaccine supply, relative to demand, is limited, planning and effective communication are critical to ensure timely delivery of vaccine to those who need it. HHS's current draft plan lacks some key information for planning our nation's response to a pandemic. It is important for the federal government and the states to work through critical issues—such as how vaccine will be purchased, distributed, and administered; which population groups are likely to have priority for vaccination; what communication strategies are most effective; and how to address issues related to vaccine and antiviral supply and hospital and workforce capacity—before we are in a time of crisis. Although HHS contends that agency flexibility is needed during a pandemic, until key federal decisions are made, public health officials at all levels may find it difficult to plan for an influenza pandemic, and the timeliness and adequacy of response efforts may be compromised.

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

GAO Contact and Staff Acknowledgments

For further information about this testimony, please contact Marcia Crosse at (202) 512-7119. Jennifer Major, Nick Larson, Gay Hee Lee, Kim Yamane, George Bogart, and Ellen W. Chu made key contributions to this statement.

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Mr. SHAYS. Thank you very much for your statement, Dr. Crosse. Ms. Selecky.

STATEMENT OF MARY C. SELECKY

Ms. SELECKY. Thank you, Mr. Chairman and distinguished members of the House Government Reform Committee. I am Mary Selecky, Washington State Secretary of Health, and I am testifying in front of you on behalf of the Association of State and Territorial Health Officials [ASTHO]. I would like to thank the Chair and the committee for continuing to focus attention on our Nation's preparedness levels and our ability to respond to a flu pandemic.

In the last year, my colleagues from Virginia and Arkansas have testified before this committee about the challenges public health leaders across the Nation faced during this past year's flu season.

My colleagues suggested three actions that the Federal Government should consider to avoid a repeat of last year's situation: first, the development of a national plan to deal with vaccine shortages; second, the establishment of a Vaccine for Adults Program; third, the expansion of funding for the Centers for Disease Control and Prevention's National Immunization Program. These three actions will help ensure that all our underserved citizens receive the vaccines they need and allow States and localities to enhance adult immunization programs. ASTHO continues to strongly urge the Congress and the administration to support these efforts.

I would like to focus my remarks on pandemic flu preparedness.

Lessons learned from last annual influenza season, the history of influenza pandemics, and the 2001 anthrax attacks continue to underscore the need for public health preparedness. Health officials must have overall preparedness plans in place, an advanced understanding of our unique role during an influenza pandemic, and a knowledge of the resources available to help us protect the public. State health officials will be looked to as controlling health authorities by Governors, legislatures, and the public they all serve. State and local health officials will need to assert significant leadership to mobilize and sustain private and public healthcare response during an influenza pandemic.

It will take Federal, State, and local public health agencies working cooperatively to deal effectively and efficiently with a public health concern of this magnitude. To date, the collaboration has been good.

We do remain concerned, however, that public health agencies have been asked to take on pandemic flu activities on top of existing priorities already established for the preparedness cooperative agreements. If the Federal Government is truly committed to enhancing our pandemic flu response, we need significant increases in resources for State and local efforts. All the preventive and therapeutic measures in the world are useless without the ability to get them to those who desperately need them.

Development of national guidelines is critically important to ensure consistent response. However, they must be flexible in order to meet State needs.

There is already significant work going on. ASTHO, our organization, produced in 2002 a preparedness planning for State health officials on pandemic influenza. States are required to have our

pandemic flu plans completed in July 2005, and Washington State completed ours in April. This has been very difficult because the Federal plan hasn't been completed, as you have heard.

Having a good plan is the first step. But exercising the plans to see what works and what needs to be improved is just as important.

In Washington State, we recently conducted a pandemic flu tabletop exercise with our neighbors to the north in Vancouver, British Columbia. In addition, Public Health Seattle King County, our largest local health jurisdiction, held a pandemic tabletop exercise with major healthcare facilities in the community as well as other county agencies.

We have unprecedented opportunity to improve the Nation's response to flu pandemic. This is an integral part of our overall preparedness. It is impossible to predict when a pandemic will occur and challenge us. But this is the wrong time for the Federal Government to cut State and local preparedness funding by $130 million, when we are to address this national priority issue.

States have plans for potential public health threats, including pandemic flu. We are exercising those plans. We will continue to improve upon them. We are making progress. Are we fully prepared? Absolutely not. We are more prepared today than we were several years ago, but not prepared enough.

The new Trust for America's Health report estimates that more than half a million Americans may die in a pandemic. Our families, our neighbors, and all the people of this country expect us to be ready when the time comes. I have no doubt that the work we are doing at the State and local level, as well as with our Federal colleagues, will help us save lives tomorrow. Please help us make sure we have the resources to get the job done.

In closing, let me reiterate four important points: pandemic flu preparedness is a critical issue for public health to address as part of its overall prevention, detection, and response efforts to any natural or terrorist event; collaboration among all levels of governmental public health is essential; reducing Federal funding for preparedness is exactly the wrong thing to do at this time—a sustained Federal commitment to preparedness is vital—and progress has been made, but there is much more to be done.

The public health community stands ready to work with you to address this threat, but we need your help and support.

I would be pleased to answer any questions you might have. Thank you, Mr. Chairman.

[The prepared statement of Ms. Selecky follows:]

Statement of

MARY C. SELECKY
SECRETARY
WASHINGTON STATE DEPARTMENT OF HEALTH

Before the

UNITED STATES HOUSE OF REPRESENTATIVES

GOVERNMENT REFORM COMMITTEE

JUNE 30, 2005

Representing

THE ASSOCIATION OF STATE AND TERRITORIAL HEALTH OFFICIALS
(ASTHO)

Mr. Chairman and distinguished members of the House Government Reform Committee, I am Mary C. Selecky, Secretary of the Washington State Department of Health, and I am honored to be appearing before you today on behalf of the Association of State and Territorial Health Officials (ASTHO). I would like to thank the Chair and the Committee members for continuing to focus attention on our nation's preparedness levels and our ability to respond to a flu pandemic.

In the last year, my colleagues from Virginia and Arkansas have testified before this committee about the challenges public health leaders across the nation faced during this past year's flu season.

My colleagues suggested three actions that the federal government should consider to avoid a repeat of last year's situation – 1) development of a national plan to deal with vaccine shortages; 2) establishment of a Vaccine For Adults Program; and 3) expansion of funding for the Centers for Disease Control and Prevention's (CDC) National Immunization Program. These three actions will help to ensure that all our underserved citizens receive the vaccines they need and allow states and localities to enhance adult immunization programs. ASTHO continues to strongly urge the Congress and the Administration to support these efforts.

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Lessons learned from the last annual influenza season, the history of influenza pandemics, and the 2001 anthrax attacks continue to underscore the need for public

health preparedness. Health officials must have overall preparedness plans in place, an advanced understanding of our unique role during an influenza pandemic, and a knowledge of the resources available to us to protect the public. State health officials will be looked to as a controlling health authority by governors, legislatures, and the public they all serve; state and local health officials will need to assert significant leadership to mobilize and sustain private and public healthcare response during an influenza pandemic.

It will take federal, state and local public health agencies working cooperatively to deal effectively and efficiently with a public health concern of this magnitude; to date, that collaboration has been good.

We do remain concerned, however, that public health agencies have been asked to take on pandemic flu activities on top of existing priorities already established for the federal preparedness cooperative agreement funding. If the federal government is truly committed to enhancing our pandemic flu response, we need significant increases in resources for state and local efforts. Vaccines and antivirals are an important part of the answer, but not nearly enough by themselves. All the preventive and therapeutic measures in the world are useless without the ability to get them to those who desperately need them.

Development of national guidelines is critically important to ensure a consistent response across the country. However, these guidelines must be flexible enough to allow each state to address its specific needs and essential services.

There is already significant work going on at the state level. States are required to have pandemic flu plans completed in July 2005. This has been very difficult because the federal plan hasn't been completed and is unavailable for use as a guide for state planners.

Having a plan is a good first step. Exercising those plans to see what works and what needs to be improved upon is just as important. In Washington State, we recently conducted a pandemic flu tabletop exercise with our neighbors to the north in Vancouver, British Columbia, Canada. In addition, Public Health Seattle King County, our largest local health jurisdiction, held a pandemic tabletop exercise with major health care facilities in the community, as well as other county agencies.

We have an unprecedented opportunity to improve the nation's response to future pandemics. Pandemic flu preparedness must be an integral part of overall preparedness. It is impossible to predict when the next influenza pandemic will occur and challenge us to respond. We must now devote significant time and resources to addressing this priority issue. This is exactly the wrong time for the federal government to cut state and local preparedness funding by $130 million.

States have plans for many potential public health threats including pandemic flu. We are exercising those plans and will continue to improve upon them. We are making progress. Are we fully prepared to respond to an influenza pandemic? Absolutely not! We are more prepared today than we were several years ago, but we are not prepared enough.

The new Trust for America's Health report estimates more than half a million Americans may die in a pandemic. Our families, our neighbors, and all the people of this country expect us to be ready when that time comes. I have no doubt that the work we do today can save lives tomorrow. Please help us make sure we have the resources to get the job done right.

In closing, let me reiterate four important points: 1) Pandemic flu preparedness is a critical issue for public health to address as part of its overall prevention, detection, and response efforts for any natural or terrorist event; 2) Collaboration among all levels of governmental public health is essential for influenza pandemic preparedness; 3) Reducing federal funding for preparedness is exactly the wrong thing to do at this time – a sustained federal commitment to preparedness is vital; and, 4) Progress has been made, but there is much more to be done.

The public health community stands ready to work with you to address this threat. We need your help and your support.

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

Chairman TOM DAVIS. Thank you very much.

Dr. Hearne. Thanks for being with us.

STATEMENT OF DR. SHELLEY A. HEARNE

Dr. HEARNE. Thank you. Mr. Chairman and members of the committee, thanks for this opportunity to present our views on preparedness.

Let me just say thank you again for being here to present our views on the potentials of what a deadly and massive novel virus could do if it hit this country. As a national organization that is dedicated to preventing epidemics and protecting people, Trust for America's Health provides the independent oversight on our Nation's public health system, that is, the front lines in a pandemic.

What we have been talking about here today is that a pandemic is actually potentially even more threatening than bioterrorism attacks, and worse is experts believe it is inevitable. Yet, what we do know is that with proactive coordinated actions, this Nation could be taking lifesaving efforts today to mitigate the devastating impact.

What I would like to do is submit for the record our just-released report "The Killer Flu?" What this report does is provide a State-by-State examination of how many people may die, how many may be hospitalized during a pandemic. It also includes a review of the United States and State preparedness, and a series of recommendations for improving readiness.

Chairman TOM DAVIS. And, without objection, that will be put in the record.

[NOTE.—The information referred to is on file with the committee.]

Dr. HEARNE. Thank you, Mr. Chairman.

Let me summarize. That report finds that there is a failure to establish a cohesive, rapid, and, most importantly, transparent U.S. pandemic strategy, which puts Americans needlessly at risk. I would like to highlight three shortcomings for you and offer some concrete suggestions on how we can actually improve the Nation's response capacity.

First, a final and operational pandemic plan must become a priority for this administration. The good news is, as was discussed, HHS has released a draft plan last August. Bad news is it is draft and with no formal deadline for completion. TFAH has actually reviewed the majority of State pandemic plans and found widely different stages of readiness.

It is no surprise, as we have discussed, since there isn't Federal guidance out there. What we have found is that most of these plans are simply plans for plans. Some States are not making those plans public, which many experts believe is going to harm our ability to fully integrate and create trust with the public, healthcare providers, and the critical first responders that would be part of a pandemic response.

To ensure nationwide preparedness standards and to facilitate a regional coordination, much like what Ms. Selecky was talking about, we need to have CDC formally reviewing and approving all State plans, and to require that these are public documents. All these plans must have greater specificity, which also was discussed

in terms of things like who are the high priority populations that would get the limited medicines and vaccines during a pandemic. Is it the healthcare workers and their families, utility operators, police, firemen?

These are the kinds of issues that we need to determine prior to an outbreak, not in the midst of crisis. Last year's flu vaccine shortage was an ugly glimpse into the lack of planning and preparedness.

And the Federal pandemic plan cannot just be a game plan for the health world. Unlike other nations, the United States does not appear to have assessed or planned how a pandemic would actually disrupt the economy and society with potential school and workplace closures and travel restrictions. The President should designate a senior official—you should have an answer when you ask who is in charge—that is responsible for ensuring that cabinet level coordination of the Federal Government's response to a pandemic.

The second issue I want to touch on is getting this Nation positioned to rapidly provide vaccines to all Americans. We are behind the eight ball because of our Nation's limited and antiquated capacity. Most experts estimate on the extensive lag time that would be existing for getting vaccines. First thing we should be thinking about: the FDA needs to immediately begin work with potential manufacturers of a vaccine to develop in advance the criteria for a rapid response approval.

We are also concerned about the U.S. domestic production capacity. With a projected stockpile of 40 million doses as a start, we need to be able to vaccinate the entire U.S. population. What HHS should be doing is investigating the value of creating a reserve manufacturing capacity here in the United States, similar to what Canada has done. This would be especially important if the pandemic is not this avian flu, which means that the current stockpile that we have of H5N1 would be ineffective.

Third, we need to assure that our stockpile of medical supplies and medicines—which many of these are being produced overseas, and with a healthcare system that relies on a "just in time" inventory—we need to be looking at how to make sure the stockpile is built faster and is large enough to cover us in the time of need.

For example, the United States is very late and very short in purchasing significant quantities of Tamiflu. Other countries have followed the who estimates of a pandemic effecting at least 25 percent of the population, and they have ordered that much. The United States is somewhere below 2 percent.

Vaccines and antivirals are not the only stockpile needs. We need to be talking about ventilators, masks, vaccines, even the vaccine injection devices that were brought up earlier.

We are also deeply concerned about the current licensing dispute that is going on between Gilead and Roche, and making sure that this does not result in a reduction of the production of Tamiflu. We urge the administration to aggressively step in and work with these companies to make sure current capacity is maintained and that we actually increase domestic operations in the immediate future.

The administration and Congress must find the sufficient funding in the coming years to increase the stockpiles and create incen-

tives for U.S.-based production. But I cannot emphasize more strongly enough the point that ASTHO and others have raised, that these pandemic activities need to be supported at all levels, but not come at the expense of other preparedness efforts. The Nation's stockpile, the preparedness activities, the bioterrorism readiness, these have to be done in a fully integrated fashion, not in separate silos and not syphoning off dollars to take care of each other.

In summary, there are several steps that we need to take today to improve readiness. It can't be a paper chase, it needs to be a priority. Thank you for the time.

[The prepared statement of Dr. Hearne follows:]

Written Testimony of

Shelley Hearne, DrPH
Executive Director
Trust for America's Health

Submitted to

U.S. House of Representatives
Committee on Government Reform

June 30, 2005

The Next Flu Pandemic: Evaluating U.S. Readiness

For further information:
Richard S. Hamburg
Director of Government Relations
Trust for America's Health
202-223-9876 (ph)
rhamburg@tfah.org

Mr. Chairman and members of the Committee, thank you for the opportunity to provide our views on *The Next Flu Pandemic: Evaluating U.S. Readiness*. As a non-profit, non-partisan organization dedicated to saving lives by protecting the health of every community and working to make disease prevention a national priority, Trust for America's Health (TFAH) maintains that proactive, coordinated public health actions can help mitigate the impact of a pandemic influenza outbreak.

TFAH has just released a report, *"The Killer Flu?,"* that provides a state-by-state examination of potential deaths and hospitalizations due to a flu pandemic based on model estimates; a state-by-state examination of capacity to treat citizens with recommended antivirals based on model estimates; a review of United States and state pandemic readiness, including a comparison to other nations' progress; and recommendations for improved pandemic readiness. I would like to submit the report in its entirety for the hearing record.

Overall, the report finds that despite the health and economic implications of such an event, pandemic planning efforts are lagging in the U.S., especially when compared to the United Kingdom (U.K.) and Canada.

The report also points out that the U.S. has not assessed or planned for the disruption a flu pandemic could cause both to the economy and society as a whole. This includes daily life considerations, such as potential school and workplace closures, potential travel and mass transit restrictions, and the potential need to close businesses resulting in complications in the delivery of food and basic supplies to people. Daily life and economic problems would likely emerge in the U.S. even before the pandemic flu hit the country due to the global interdependence of the world economy.

An equally troubling finding establishes that aspects of the planning process, such as ensuring vaccine and antiviral capabilities and surge capacity readiness, are incomplete or fragmented.

Mr. Chairman, TFAH maintains that the failure to establish a cohesive, rapid, and transparent U.S. pandemic strategy could prove a major weakness against a virulent and efficient virus -- putting Americans needlessly at risk.

That is why we believe that Congress and the Administration must take steps now to ensure that the nation's public health system and the health care delivery system will be able to respond to a major health crisis -- even beyond some of our fears of bioterrorism or chemical terrorism. While experts predict a pandemic flu may be "inevitable," subsequent death rates predicted to be in the millions are not. What will make the difference? We need strong, directed and rapid federal leadership, we must convert national and state pandemic influenza plans into operational blueprints, and we should increase vaccine production and capacity, procure adequate vaccines and antivirals for treatment, and stockpile additional medical supplies and equipment.

Pandemic Readiness: Moving from Planning to Action

Mr. Chairman, simply put, U.S. pandemic influenza preparedness is inadequate. Both the federal pandemic plan and various state pandemic plans are insufficient blueprints for an effective national response to a pandemic influenza.

Although a positive first step, the federal pandemic flu plan issued last August by the Department of Health and Human Services (DHHS) is still a draft. Moreover, the draft plan lacks specificity in several key areas, which were enumerated in comments received by the Department during the public comment period. TFAH believes that a final pandemic influenza plan must become a priority for this Administration and should provide the operational blueprint for the six pandemic phases as defined by the World Health Organization (WHO).

At the state level, most public health agencies have developed draft pandemic response plans, but they are in widely different phases of readiness. Many states have asked for additional and more specific guidance from the DHHS. Some are refusing to make their plans public even though many experts believe that public availability of plans is essential to improve integration with other jurisdictions, health care providers, and first responders.

TFAH believes that the Centers for Disease Control and Prevention (CDC) should formally review and approve state pandemic influenza plans in order to ensure nationwide preparedness standards and to facilitate regional coordination. Further, we urge CDC to require states to make approved plans publicly available. Perhaps most importantly, TFAH believes that pandemic flu preparedness activities at the federal, state and local levels should be supported with specific funding and not come at the expense of other preparedness efforts.

At the beginning of a pandemic, there may be an insufficient supply of vaccines and antivirals. A key element of pandemic planning is to determine protocols for allocation of vaccines and medicines among high priority populations, such as health care workers and public safety workers, prior to an outbreak.

As we learned last winter, prioritization is also important for the annual flu, when vaccine is in short supply. With the recent announcement by Chiron that its manufacturing capacity for this year's influenza vaccine will fall short, it would be prudent for CDC and DHHS officials to provide specific guidance now to states' health agencies as to which sectors of the population should receive antiviral medications and vaccines. In addition, CDC should immediately put into place measures that would assure equal geographic access to vaccines so that the nation does not face a shortage of annual influenza vaccine, with some states having excess supply and others unable to meet the demand for high-risk groups. This would help prevent the widespread confusion, long lines of worried elderly Americans, and the vaccine distribution issues that plagued last year's flu season.

With respect to federal leadership, TFAH urges the President to designate a senior official, whose primary responsibility is to assure Cabinet-level coordination of the federal government's response to a pandemic and also to ensure coordination between civil society (non-governmental economic infrastructure) and government during a pandemic.

Ultimately, there should be a government-wide pandemic preparedness plan, not just one that centers on health-related matters and DHHS activities.

Further, we believe that the CDC, in consultation with other federal agencies, should develop and implement a public education campaign about pandemic influenza and preparedness, including information on the potential need for general vaccination and personal precautionary measures. The agency should also develop a plan for communicating with the business community to provide information about the potential economic consequences of a pandemic, including the possibility of mass absenteeism and the potential need to convert certain facilities (e.g. hotels) as surge capacity treatment centers.

Stockpiling Vaccines, Medicines, Medical Supplies and Equipment

Building a stockpile for a pandemic is a responsible public health measure and TFAH maintains that adequate preparedness includes stockpiling *both* a vaccine and antivirals. However, we remain deeply concerned that the stockpiles will not be built fast enough and will not be large enough.

The U.S. is very late in entering the market for significant bulk purchase of Tamiflu, an antiviral that can treat symptoms of influenza and reduce the severity of the infection. With current production capacity, it could be sometime in 2007 before the stockpile ordered today is available. Most Tamiflu is produced abroad and requires nearly one year to manufacture. We believe that the Department should take immediate steps to work with industry to increase domestic production capacity, to assure that the stockpile is built quickly, and to assure that in the event of a pandemic Tamiflu will continue to be available to Americans.

It is also not clear that the amount of Tamiflu ordered is sufficient to address the demand in a pandemic. Other countries are following WHO estimates of a pandemic affecting at least 25 percent of the population, and have ordered enough Tamiflu to treat all who might be sick. This would translate to over 70 million courses in the United States. Some, such as the Infectious Diseases Society of America, have called for stockpiling as much as 124 million courses of Tamiflu for treatment and prevention of avian flu.

TFAH remains even more concerned about vaccine production capacity. In a pandemic, we can target antiviral treatment to those who are already sick, but must provide vaccines to all who are at risk -- which in this case would be all Americans. It is not at all clear that U.S. domestic vaccine producers could rapidly manufacture hundreds of millions of doses of a pandemic flu vaccine.

Most experts estimate there will be a lag time of six to nine months before a vaccine can be produced in sufficient quantities to protect individuals against a pandemic strain of influenza to which most people will have no natural immunity. While issues around vaccine manufacturing, distribution, safety and access are complex, other nations are putting protocols in place now with respect to creating a rapid response approval process for a pandemic flu vaccine. For example, regulators in the U.K. are already working with vaccine manufacturers to develop a model application for approval of a pandemic vaccine.

TFAH believes that the Food and Drug Administration (FDA) should immediately begin work with potential manufacturers of a pandemic flu vaccine to develop in advance the specific criteria for rapid response approval of a pandemic vaccine, which might save a month or two in the time it takes from identifying the flu strain and having the capacity to vaccinate Americans.

We are also concerned about whether the U.S. has sufficient domestic production capacity for a pandemic flu vaccine. While a projected initial stockpile of 40 million doses is a start, we would need to be able to vaccinate the entire U.S. population against a pandemic strain. Only about half of the U.S. annual flu vaccine supply is generated within the U.S.; in a pandemic, products manufactured elsewhere may not be available to us. We believe DHHS should investigate the value of creating a reserve production capacity to assure rapid ramp up of production, something the Canadian government has contracted for in the event of a pandemic. This would be especially important in the event the pandemic strain is not avian flu, which means the current H5N1 stockpile would not be effective.

Therefore, we hope the Administration will work with Congress to find sufficient funding in Fiscal Year (FY) 2006 to increase stockpiles to true preparedness levels and create incentives for industry to increase U.S.-based Tamiflu and vaccine production.

Vaccines and antivirals are not the only supplies that need to be stockpiled in preparation for a pandemic. Federal officials should also address the need to stockpile medical supplies that will be necessary to combat a pandemic. Currently, most health providers order and stock supplies on a "just-in-time" basis. This means they often have only a few days of reserve supplies, equipment, and medicines, including many basic protective items, such as masks, gloves, gowns, and clean hospital linens, many of which are produced in Asia, which may be the epicenter of a pandemic. That's why we believe steps must be taken immediately to stockpile additional supplies, particularly since during an outbreak, many production and delivery systems for supplies will likely be stalled or even stopped.

Additional Recommendations

"*A Killer Flu?*" details a series of specific recommendations that would bolster U.S. readiness to combat an influenza pandemic. In addition to the recommendations related to operationalizing pandemic plans, government-wide coordination and leadership, vaccine production and the need to stockpile vaccines, antivirals and medical supplies, TFAH believes that Congress, the Administration and state health officials should take the following actions:

- **Define Roles and Responsibilities**

  A clearly-defined organizational structure and chain of command is essential for rapid and efficient control and response, both in the federal government and at the state and local levels. Immediate planning should be occurring at the federal level to minimize disruption of the health care system and the overall economy. States must define and agree upon leadership roles and responsibilities with respect to who is in charge of a state's public health and health care decisions. Plans must also designate liaisons to work with other jurisdictions and federal officials.

- **Outbreak Tracking**

  Plans should ensure adequate laboratory surveillance of influenza, including the ability to isolate and subtype influenza viruses year round. Following federal guidelines outlined by DHHS, states should report all necessary data and information to federal and other health officials as soon as it becomes available. Congress should provide additional support for CDC's global surveillance activities, and the U.S. should support the WHO's surveillance program to assure as early a warning as possible for U.S. preparedness purposes.

- **Vaccine Research, Development, and Production**

  The U.S. should continue to support and expand research into new technologies for influenza vaccine and clinical trials for potential avian flu and other pandemic vaccines. While the U.S. has issued limited contracts for stockpiling a potential pandemic vaccine, the federal government should also explore the Canadian approach of contracting for a reserve production capacity located in the U.S. A vaccine stockpiling approach is successful if public health authorities have guessed correctly on what the pandemic strain will be. A reserve production capacity can assure quick turnaround for production of a vaccine for the actual pandemic strain.

- **Mass Vaccination and Treatment Systems**

  The federal government, in coordination with the states, must develop systems for tracking and distributing antiviral medication and vaccines. A national system is needed to assure targeted and/or equitable distribution of supply, so we do not have a repeat of the 2004-2005 flu season distribution problems. State-level systems also are needed to assure similar availability across a state. One of the best ways to improve vaccination preparations for a pandemic outbreak may be to enhance annual flu vaccination coverage for non-traditional high-risk groups (e.g. individuals with chronic diseases or compromised immune systems) to facilitate access to these populations.

- **Public Information Campaigns and Materials**

  Communicating with the public in a clear and efficient manner is essential during a high-anxiety time. The federal government, in conjunction with the states, should develop coordinated messages for various audiences (media, public, providers, etc.) for each stage of a potential pandemic. States must identify and train spokespersons in multiple languages and educate public health officials, politicians, community leaders, partners, and the media about what information will and will not be available during a pandemic. States should ensure clear and consistent messaging by creating information templates in multiple languages ready for customization and distribution during a pandemic.

- **Surge Capacity Capabilities**

  Plans must account for the likelihood that hospitals will be quickly overwhelmed during a pandemic, by developing auxiliary sites such as shelters, schools, nursing homes, hotels, and daycare centers for surge capacity treatment and for treatment of the "walking well." States should be conducting surveys of potential sites and obtaining agreements.

- **Secure a Backup Workforce**

  States should conduct and maintain an inventory of healthcare professional residents, including current and retired doctors, nurses, veterinarians, emergency medical staff, and other potential volunteers. These workers could be an essential expanded workforce during a pandemic. Pandemic survivors are also a population of potential workers. States should plan for tracking and soliciting volunteer support from this population, which is presumably immune to the virus.

- **Ensure Availability of Food, Water, and Other Supplies**

  States must account for high demand for food, water, and other basic supplies, and plan for distribution to general and hard-to-reach populations. Plans should factor in potential complications that include: infected food and delivery workers, possible infected store facilities, and limitations on public interaction both for those infected and the general population at risk of exposure. Planners must also weigh the issue of "just-in-time" manufacturing of food and supplies, since reserves of supplies will not be available. Additionally, planners must address the limitations of medical equipment manufacturing, much of which Asia exports to the world.

- **Quarantine Measures and Authority to Close Public Places**

  States must establish clear legal authority and emergency measures to effectively contain the spread of disease. States must have powers to prohibit public gatherings, close public facilities and schools, and restrict travel, if necessary.

- **Measures to Manage Mass Death**

  Planning for worst-case scenarios is a critical component of effective planning. States must conduct and maintain an inventory of facilities with sufficient refrigerated storage to serve as temporary morgues in the event of a pandemic.

Such policies and investments will help stabilize the nation's health and economy in the event of a pandemic while ensuring that pandemic readiness preparations are "commensurate with the scale of the threat we face."

I thank you again for this opportunity to express TFAH's views on evaluating U.S. readiness for the next flu pandemic.

Chairman TOM DAVIS. Thank you very much.

Dr. Milligan, thank you for being with us.

STATEMENT OF DR. JOHN F. MILLIGAN

Dr. MILLIGAN. Mr. Chairman, Congressman Waxman, and committee members, thank you for the invitation to present here today. I am John Milligan, executive vice president and CFO of Gilead Sciences. By way of background, I am a Ph.D. biochemist, and I was a project team leader for the development of Tamiflu by Gilead.

Gilead is a biopharmaceutical company headquartered in Foster City, CA, the district of Congressman Tom Lantos. We also have research facilities in Durham, NC; a manufacturing facility in San Dimas, CA; and overseas offices throughout Europe and Australia.

Since Gilead was founded nearly 20 years ago, the company has focused on advancing the care of patients suffering from life-threatening diseases. Over the course of our company's history, Gilead has successfully developed, commercialized, and ensured broad access to a portfolio of antiviral medicines in HIV and hepatitis.

Today, these important antivirals are improving the quality of life for patients around the globe. Gilead does not achieve this alone, but through a strong commitment to collaboration, working in partnership within our industry, with governments, with healthcare professionals, and with nongovernmental organizations.

As you know, Gilead is the inventor of Tamiflu, or oseltamivir phosphate. Tamiflu is the first and only antiviral pill available for the treatment and prevention of all common strains of influenza A and B. The compound was shown to be active in animal models against avian flu, also known as H5N1 strain of the virus. Tamiflu was discovered by Gilead scientists in 1996, and Gilead conducted all the initial characterization of the compound and developed the manufacturing process for the product.

Also in 1996, Gilead entered into an exclusive agreement with F. Hoffman-La Roche of Basel, Switzerland, providing for the development and commercialization of Tamiflu worldwide. According to the agreement's terms, Gilead and La Roche collaborated on Tamiflu's clinical development, with Gilead successfully managing three out of the four registrational trials leading to FDA approval. Since the U.S. product launch in late 1999, however, La Roche has been solely responsible at its own expense for product commercialization, including manufacturing, marketing, and distribution "in substantially all markets of the world."

While vaccination is the primary weapon in combating influenza, we believe Tamiflu is a key component in addressing the potentially devastating impact of the disease. The role of Tamiflu must be better recognized, not just for pandemic planning, but also for seasonal influenza outbreaks. It bears emphasis that Tamiflu is not just effective for treatment of influenza, but also effective for influenza prophylactic, meaning it can prevent transmission of the virus.

Since at least 2001, we believe that our partner Roche has neither demonstrated acceptable commitment nor dedicated adequate resources to Tamiflu.

Chairman TOM DAVIS. Dr. Milligan, we are really not interested in the corporate disputes. If we could move on. We are really interested in your product, and the fact that you and Roche can work out your problems and make sure that we get this to market.

Dr. MILLIGAN. I agree. At the heart of this, this is a commercial issue between the two companies, and not an action that we take lightly. I want to underscore an important point, which is that this action will not affect current arrangements or planning for the manufacture and supply of Tamiflu.

Roche is responsible, and will be responsible, for ongoing manufacturing, until time such time as the termination of the agreement becomes effective. The agreement also explicitly provides that in the event of termination, Roche must continue to supply product for up to 2 years and must transfer necessary manufacturing technology to Gilead.

Consequently, Gilead anticipates a coordinated and orderly process for the transfer of manufacturing, should termination occur. During any period of transition thereafter, Gilead will honor the supply obligations undertaken by Roche.

I would like to be especially clear about Gilead's commitment to advancing the care of patients suffering from diseases. In the mid and late–1990's, Gilead conducted extensive research on oral neuraminidase inhibitors, the class of drug to which Tamiflu belongs. We moved Tamiflu into clinical evaluation because, among the compounds we tested, it had the best potential safety and efficacy profile.

In accordance with our 1996 contract with Roche, Gilead continued to conduct extensive research into various compounds that showed activity against influenza A and B. Many structural classes were identified; however, none of these were thought to have better properties than Tamiflu, and none are currently being pursued as viable options for the treatment and prevention of influenza. Any of these compounds would be included in the 1996 agreement between Gilead and Roche, and Gilead would not be free to pursue any of these on its own.

I also want to highlight that Gilead is a leader in the manufacturing of antiviral medicines at large scales. Our expertise drawn from experience with HIV therapeutics is highly relevant to the situation surrounding the influenza pandemic. Gilead has and is continuing to manage the manufacturing of our HIV products in amounts that well exceed 2004 and anticipated 2005 production volumes for Tamiflu.

Comparable to the unpredictability of flu pandemics, the rapidly growing global HIV epidemic has required a carefully structured manufacturing plan for antiretrovirals, in absence of accurate forecasts estimating the number of patients to be treated for HIV resource-limited countries for years to come. Further, before issuing the notice of termination, Gilead conducted a thorough internal assessment of our capabilities. We determined that we can meet the global pandemic and seasonal needs for Tamiflu and make significant contributions in advancing manufacturing, supply, and medical education for this important antiviral medicine.

At Gilead, we believe that important lessons can be learned from previous annual influenza seasons, particularly with regard to the

administration of Tamiflu. If the effort is made to study the facts and data available to us, and to engage with leaders in global public health, these lessons can and should be applied to enhance responses to both seasonal and pandemic flu.

For instance, much attention has been drawn to the fact that in order to be most effective for combating influenza, Tamiflu must be taken within 48 hours of exposure to the virus. It is true that this 48-hour window is absolutely critical to ensure better outcomes for the infected individuals and the existence of this window highlights the importance of advancing education, securing supply, and breaking down the barriers to rapid access to the product. In order to underscore this crucial point, I have made available to the members of the committee a paper published by the Journal of Antimicrobial Chemotherapy on the benefits of early administration of Tamiflu.

Our role, should Tamiflu rights be returned to Gilead, will be one of planning and partnership. We believe there is an urgent need for increased education about and access to Tamiflu, not only for pandemic purposes, but as importantly for seasonal influenza.

Gilead looks forward to establishing partnerships with the distinguished committee members and government agency representatives here today, and with governments and public health officials around the world. We are prepared to enter into constructive dialog about the important role of Tamiflu in global public health, which we intend to fully support with appropriate, constructive action. Thank you.

[The prepared statement of Mr. Milligan follows:]

United States House of Representatives
Committee on Government Reform
Testimony of John F. Milligan, PhD
Executive Vice President and Chief Financial Officer, Gilead Sciences, Inc.
June 30, 2005

Mr. Chairman, Congressman Waxman, Committee Members – thank you for the invitation to be here today. I am John Milligan, Executive Vice President and Chief Financial Officer of Gilead Sciences. By way of background, I am a PhD biochemist by training, and I was the project team leader for the development of Tamiflu® by Gilead.

About Gilead Sciences

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Since Gilead was founded nearly 20 years ago, the company has focused on advancing the care of patients suffering from life-threatening diseases. Over the course of our company's history, Gilead has successfully developed, commercialized and ensured broad access to a portfolio of antiviral medicines in HIV and hepatitis. Today, these important antivirals are improving the quality of life for patients around the globe. Gilead does not achieve this alone, but through a strong commitment to collaboration – working in partnership within our industry, with governments, with health care professionals and with nongovernmental organizations.

Development of Tamiflu (oseltamivir phosphate) – Gilead's Role

As you may know, Gilead is the inventor of Tamiflu, or oseltamivir phosphate. Tamiflu is the first and only antiviral pill available for the treatment and prevention of all common strains of influenza A and B. The compound has been shown to be active in animal models against avian flu, also known as the H5N1 strain of the virus. Tamiflu was discovered by Gilead scientists in 1996, and Gilead conducted all the initial characterization of the compound and developed the manufacturing process for the product.

Also in 1996, Gilead entered into an exclusive agreement with F. Hoffmann-La Roche of Basel, Switzerland, providing for the development and commercialization of Tamiflu worldwide. According to the agreement's terms, Gilead and Roche collaborated on Tamiflu's clinical development, with Gilead successfully managing three out of the four registrational trials leading to FDA approval. Since the U.S. product launch in late 1999, however, Roche has been solely responsible, at its own expense, for product commercialization, including manufacturing, marketing and distribution "in substantially all markets of the world."

While vaccination is the primary weapon in combating influenza, we believe Tamiflu is a key component in addressing the potentially devastating impact of the disease. The role of Tamiflu must be better recognized not just for pandemic planning, but also for seasonal influenza outbreaks. It bears emphasis that Tamiflu is not just effective as a treatment for influenza

patients, but is also an effective influenza prophylactic, meaning it can prevent transmission of the virus. Each year, influenza results in 3 to 5 million cases of severe illness and 250,000 to 500,000 deaths worldwide. In the United States alone, up to 40 million Americans develop the flu, more than 200,000 people are hospitalized and 36,000 people die as a result of the flu and its complications during the average flu season.

Gilead's Partnership with Roche – June 2005 Notice of Termination

Since at least 2001, we believe that our partner, Roche, has neither demonstrated acceptable commitment, nor dedicated adequate resources to Tamiflu. This has led to a lack of awareness of the product and its benefits by health care professionals.

On June 23, Gilead delivered to Roche a notice of termination for material breach of our 1996 Agreement. Gilead's decision to terminate the agreement follows the communication of the company's concerns over a period of several years – concerns communicated repeatedly, without results. We believe our decision to provide notice of termination of the 1996 Agreement is justified by the following material breaches: (1) Roche has failed to use best efforts to commercialize Tamiflu by adequately promoting and marketing the product in a sustained manner in all significant markets; and (2) Roche has failed to use best efforts to commercialize Tamiflu, evidenced by past problems with the manufacturing process that led to recalls and shortages in product supply; and (3) Roche has failed to pay all royalties fairly owed to Gilead.

At its heart, this is a commercial issue between two companies. This is not an action we take lightly. Our actions – and I want to underscore this important point – will not affect current arrangements or planning for the manufacture and supply of Tamiflu. Roche is responsible and will be responsible for ongoing manufacturing until such a time as the termination of our Agreement becomes effective. The Agreement also explicitly provides that, in the event of termination, Roche must continue to supply product for up to two years and must transfer necessary manufacturing technology to Gilead. Consequently, Gilead anticipates a coordinated and orderly process for the transfer of manufacturing, should termination occur. During any period of transition and thereafter, Gilead will honor the supply obligations undertaken by Roche.

I'd like to be especially clear about Gilead's commitment to advancing the care of patients suffering from life-threatening infectious diseases. In the mid and late 1990s Gilead conducted extensive research on oral neuraminidase inhibitors – the class of drug to which Tamiflu belongs. We moved Tamiflu into clinical evaluation because among the compounds we tested, it had the best potential safety and efficacy profile. In accordance with our 1996 contract with Roche, Gilead has continued to conduct extensive research into various compounds that have shown activity against influenza A and B. Many structural classes were identified, however, none of these were thought to have better properties than Tamiflu and none are currently being pursued as viable options for the treatment and prevention of influenza. Any of the compounds would be included in the 1996 agreement between Gilead and Roche, and Gilead would not be free to pursue these on its own.

Manufacturing Expertise

I want to also highlight that Gilead is a leader in the manufacture of antiviral medicines at large scales. Our expertise drawn from experience with HIV therapeutics is highly relevant to the situation surrounding a potential influenza pandemic. Gilead has and is continuing to manage the manufacturing of our HIV products in amounts that well exceed 2004 and anticipated 2005 production volumes for Tamiflu. Comparable to the unpredictability of flu pandemics, the rapidly growing global HIV epidemic has required a carefully structured manufacturing plan for

antiretrovirals, in absence of accurate forecasts estimating the number of patients to be treated for HIV in resource-limited countries in years to come. Further, before issuing the notice of termination, Gilead conducted a thorough internal assessment of our capabilities. We determined we can meet the global pandemic and seasonal needs for Tamiflu and make significant contributions in advancing manufacturing, supply and medical education for this important antiviral medicine.

Need for Ongoing Education

At Gilead, we believe that important lessons can be learned from previous annual influenza seasons – particularly with regards to the administration of Tamiflu. If the effort is made to study the facts and data available to us, and to engage with leaders in global public health, these lessons can and should be applied to enhance responses to both seasonal and pandemic flu events.

For instance, much attention has been drawn to the fact that, in order to be most effective for combating influenza, Tamiflu must be taken within 48 hours of exposure to the virus. It is true that this 48-hour window is absolutely critical to ensure better outcomes for the infected individuals and the existence of this window highlights the importance of advancing education, securing supply and breaking down barriers to rapid access to the product. In order to underscore this crucial point, I have made available to the Members of the Committee a paper published by the *Journal of Antimicrobial Chemotherapy* (accepted on September 24, 2002) on the benefits of early administration of Tamiflu.

Gilead's Commitment to Partnership

Our role, should rights to Tamiflu be returned to Gilead, will be one of planning and partnership. We believe that there is an urgent need for increased education about and access to Tamiflu – not only for pandemic planning purposes, but as importantly for seasonal influenza.

Gilead looks forward to establishing partnerships with the distinguished committee members and government agency representatives here today, and with governments and public health officials around the world. We are prepared to enter into constructive dialogue about the important role of Tamiflu in global public health, which we intend to fully support with appropriate, constructive action. Thank you.

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Early administration of oral oseltamivir increases the benefits of influenza treatment

F. Y. Aoki[1]*, M. D. Macleod[2], P. Paggiaro[3], O. Carewicz[4], A. El Sawy[5], C. Wat[6], M. Griffiths[6], E. Waalberg[7] and P. Ward[6] on behalf of the IMPACT Study Group†

[1]*University of Manitoba, Room 510–730 William Avenue, Winnipeg, Canada;* [2]*Aldershot Health Centre, Aldershot;* [6]*Roche Global Development, Welwyn, UK;* [3]*Cardiothoracic Department, Cisanello Hospital, Pisa, Italy;* [4]*Dossenheim, Germany;* [5]*Euraxi, Saint Martin d'Heres, France;* [7]*F. Hoffmann-La Roche, Basel, Switzerland*

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Our objective was to evaluate the benefit of early treatment of influenza illness using oral oseltamivir. This open-label, multicentre international study investigated the relationship between the interval from illness onset to first dose (time-to-treatment) and illness duration in the intent-to-treat infected population using accelerated failure time (AFT) modelling. A total of 1426 patients (12–70 years) presenting within 48 h of the onset of influenza symptoms were treated with oseltamivir 75 mg twice a day for 5 days during the 1999–2000 influenza season; 958 (67%) had laboratory-confirmed influenza virus infection. Earlier intervention was associated with shorter illness duration ($P < 0.0001$). Initiation of therapy within the first 12 h after fever onset reduced the total median illness duration by 74.6 h (3.1 days; 41%) more than intervention at 48 h. Intermediate interventions reduced the illness proportionately compared with 48 h. In addition, the earlier administration of oseltamivir further reduced the duration of fever, severity of symptoms and the times to return to baseline activity and health scores. Oseltamivir was well tolerated. The most common adverse events were nausea and vomiting, which were transient and generally occurred only with first dosing. When oseltamivir was taken with food, the tolerability was enhanced. The overall discontinuation rate was low (1.8%). In conclusion, the IMPACT study demonstrated that earlier initiation of oral oseltamivir therapy increased its therapeutic effects, which were seen at every time point of intervention and were progressive. Thus, early presentation, diagnosis and treatment of patients with influenza maximized the benefits of oseltamivir therapy.

Keywords: influenza, neuraminidase inhibitors, oseltamivir, treatment

Introduction

Annual influenza outbreaks lasting for 6–8 weeks result in illness in an average of 10% of the population.[1] Influenza disrupts the normal activities of individuals and, because of the large number of people incapacitated by the illness, results in a considerable burden to society.[2,3] Increases of up to five-fold in consultations for influenza-like illness in general practice intensifies pressure on primary healthcare services.[4]

There is a need for effective and well-tolerated treatments that can reduce the impact of influenza on the individual and society. Oseltamivir is the oral prodrug of oseltamivir carboxylate, a potent inhibitor of influenza A and B viral neuraminidase. Oseltamivir is well tolerated and effective for the treatment of acute influenza in previously healthy adults.[5,6] In influenza-infected patients treated within 36 h of symptom onset, oseltamivir reduced the duration of clinical illness by 30% ($P < 0.001$), when compared with symptomatic treatment alone.[5]

The pathogenesis of influenza illness suggests that inhibiting viral replication as early as possible after infection will reduce the duration and intensity of symptoms. In the study of

*Corresponding author. Tel: +1-204-789-3625; Fax: +1-204-789-3926; E-mail: nelsonak@ms.umanitoba.ca
†Members of the IMPACT Study Group are listed in the Acknowledgements.

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Nicholson *et al.*,[6] patients starting oseltamivir within 24 h of symptom onset had a 37% reduction in illness duration compared with placebo. Studies with the inhaled influenza neuraminidase inhibitor zanamivir have also suggested the additional benefit of earlier treatment.[7,8] These findings are consistent with increased treatment benefits that result from early antiviral treatment of other viral diseases.[9,10]

The IMPACT (IMmediate Possibility to ACcess oseltamivir Treatment) study investigated the relationship between the time to intervention and duration of illness as a primary endpoint, plus other parameters of illness, by treating with oral oseltamivir as early as possible after the onset of influenza symptoms.

Materials and methods

This was a prospective, open-label, exploratory, multicentre international study conducted during the influenza season 1999–2000. During local influenza outbreaks, subjects aged ≥13–70 years presenting within 48 h of the sudden onset of fever (≥37.8°C, ≥100°F) with at least two of the following symptoms: cough, sore throat, coryza, myalgia, headache, fatigue and chills/sweats were enrolled and received oral oseltamivir 75 mg twice a day for 5 days. Volunteers were advised to take the study medication with a meal or snack, and ingestion of the first dose was observed directly and the time recorded. Those with uncontrolled chronic medical disorders were excluded as were women who were pregnant, lactating or not using a reliable method of contraception. Individuals who had HIV infection, a transplant or a clinically relevant history of abuse of alcohol or other drugs were excluded. Subjects who had experienced an acute upper respiratory tract infection (URTI), otitis media, bronchitis or sinusitis or who had been treated with an antiviral drug, systemic steroids or immunosuppressants within 2 weeks of the study start were also excluded. Influenza infection was confirmed by virus recovery from nose or throat swabs taken pre-dose and on day 3 (in selected centres only), and/or a ≥four-fold rise in serum antibody titres to influenza virus. Nose and throat swabs were transported to country-specific virology laboratories either in chilled viral transport medium within 72 h or in ambient conditions within 24 h of collection from the patient. The swabs were eluted and inoculated onto Madin–Darby canine kidney (MDCK) cell monolayers and incubated for up to 7 days. Cell-associated influenza A or B viruses were identified using immunofluorescent antibody techniques or the haemadsorption test.

Baseline and day 21 sera were assayed together by measurement of the haemagglutination-inhibition (HAI) antibody or complement fixation test (CFT) antibody. The following antigens were used for the majority of HAI assays: A/Bayern/7/95 (H1N1), A/Sydney/5/97 (H3N2), B/Yamanashi/66/98; the antigens used for CFTs were influenza A and B nucleocapsid.

Temperature and symptom scores were recorded twice daily and a health scale questionnaire was answered daily for 21 days after the start of the study.

The primary endpoint was duration of illness as a function of time to the first treatment dose, calculated from the time of onset of fever (defined as the earliest time that the patient either measured an elevated temperature or felt feverish) in the laboratory-confirmed, influenza virus-infected population. The duration of illness was defined as the time from symptom onset to alleviation of all symptoms. Duration of illness was measured from the onset of fever or when the patient felt feverish until all symptoms were scored as mild or absent and remained so for at least 24 h. Other endpoints included the severity of the influenza illness by measurement of area under the curve of total symptom scores, the times to resolution of fever (assessed as the time to return to an afebrile state, i.e. a temperature of ≤37.2°C), and return to baseline health and activity scores. Adverse events were recorded up to study day 21 (±4) and graded on a four-point scale (mild, moderate, severe, life threatening).

The study was conducted in accordance with the principles of the Declaration of Helsinki (amended) or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The protocols were approved by local or regional ethics committees prior to implementation and all participants gave written informed consent before enrolment.

Analysis of data

To determine the added value of early intervention, the relationship between time to treatment and illness duration from fever onset was analysed. The results were compared descriptively by time-to-treatment groups and also by accelerated failure time (AFT) modelling on the actual data collected.[11] The LIFEREG procedure in SAS (version 6.12) was used to perform the AFT analysis, in a Unix environment. Estimates were produced on the natural log scale, but were back-transformed for presentation in all summary tables. The error structure was modelled using the log-normal distribution, and for all best fit models, normal probability plots of the residuals were produced and examined for indications of lack-of-fit.

The median times of illness duration from illness onset are also presented for time-to-treatment groups together with 95% confidence intervals.

Kaplan–Meier curves of the duration of illness data were constructed for each time-to-treatment group in order to estimate the median duration of illness and associated 95% confidence interval along with other summary statistics.

Table 1. Summary of the demographics of the safety population

	Oseltamivir 75 mg twice a day (n = 1426)
Female, n (%)	716 (50%)
Median age (range; years)	40.0 (12–70)
Influenza virus infected, n (%)	958 (67%)
type A	944 (66%)
type B	6 (0%)
type A and B	8 (1%)
unknown	26 (2%)
Influenza vaccinated, n (%)	121 (8%)

Results

A total of 1428 patients entered the study. Of these, 1426 received study treatment and comprise the intent-to-treat (ITT) safety population (Table 1). Two 12-year-old patients, who deviated from the age inclusion criteria, were included in the ITT population. The intent-to-treat infected (ITTI) population consisted of the 958 (67%) subjects with laboratory-confirmed influenza, 955 of whom received study medication and provided data permitting calculation of the clinical endpoints. There were no major differences in infection rates between the time windows. Of the ITTI population, 140 (15%) subjects entered the study within 6 h of symptom onset, 240 (25%) within the first 12 h and 573 (60%) within 24 h.

There was a correlation between the time of intervention after symptom onset and the illness duration, such that the duration of illness was shorter the earlier treatment began (Table 2). AFT modelling of the data confirmed that earlier intervention was strongly associated with shorter illness duration ($P < 0.0001$) (Table 3 and Figure 1). Intervention within the first 12 h after fever onset reduced the median illness duration by 3.1 days more than if intervention was delayed until 48 h (Figure 2). For every 6 h earlier that oseltamivir was initiated, the predicted median illness duration was shortened by an acceleration factor of 1.09 (8%). This corresponded to a benefit of ~10 h (range 8–15) shorter duration of illness for every 6 h earlier that treatment was initiated. The outcomes based on the absolute time-to-treatment group data and those produced by the use of AFT modelling results were highly comparable.

As well as the additional benefit of early administration on illness duration, benefits were also seen in other efficacy endpoints. Earlier intervention was strongly associated with a shorter time to return to normal health ($P = 0.0001$) and baseline activity ($P = 0.0001$) (Figure 4). Earlier intervention also reduced the fever duration ($P = 0.0115$) (Figure 4) and severity of illness ($P = 0.0023$) (Figure 3). The acceleration factors for these parameters were 1.05, 1.07, 1.12 and 1.03, respectively. Approximately 90% of all influenza-infected

Table 2. Duration of illness observed in the intent-to-treat infected population (n = 955) per time-to-treatment group in patients treated with oseltamivir 75 mg twice daily for 5 days

	Duration of illness (h) between onset of symptoms and treatment start				
	0–6 (n = 140)	>6–12 (n = 100)	>12–24 (n = 332)	>24–36 (n = 258)	>36–48 (n = 125)
Median duration (h)[a] (95% CI)	81.8 (70.7–105.5)	110.2 (93.0–123.5)	111.1 (98.5–122)	127.8 (111.8–151.5)	180.0 (146.7–202.8)

[a]The time from the start of the illness to alleviation of all symptoms.

Table 3. Duration of illness predicted by the AFT model[a] in patients treated with oseltamivir 75 mg twice daily for 5 days

	Time (h) from start of illness to treatment					
	0	6	12	24	36	48
Predicted median illness duration (h)	90.7	98.9	108	128.7	153.3	182.6
Reduction in illness duration (h)[b]	91.9	83.6	74.6	53.9	29.3	NA
(95% CI)	(78.4–107.7)	(72.2–96.8)	(65.0–85.6)	(47.2–61.5)	(25.3–33.9)	
Acceleration factor[b]	2.01	1.85	1.69	1.42	1.19	NA

[a]Model contains sex, age, baseline total symptom score, vaccination status time-to-treatment, baseline total symptom score time-to-treatment interactions.
[b]Compared with initiation of therapy at 48 h after start of illness.
NA, not applicable; CI, confidence interval.

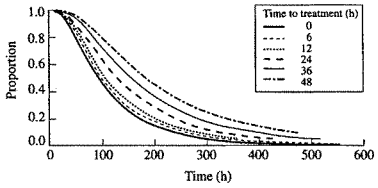

Figure 1. The duration of influenza illness is shorter the earlier that oseltamivir treatment 75 mg twice a day for 5 days is initiated (intent-to-treat infected population).

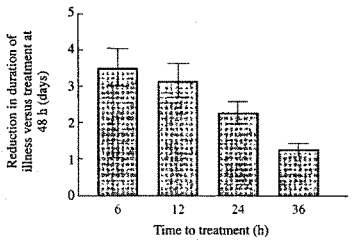

Figure 2. The reduction in days of illness duration with earlier treatment with oseltamivir 75 mg twice a day in comparison with delayed treatment at 48 h (intent-to-treat infected population). The data are median and 95% CI.

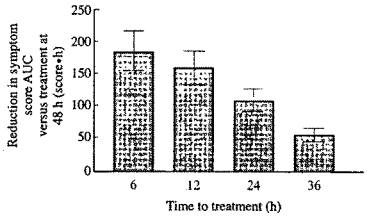

Figure 3. The reduction in total symptom score AUC with earlier treatment with oseltamivir 75 mg twice a day in comparison with delayed treatment at 48 h. The data are median and 95% CI.

patients treated with oseltamivir had a reduction of fever, <37.8°C, within 36 h of taking their first dose.

The duration of illness was seemingly shorter when intervention occurred earlier in patients who were not infected with influenza and treated with oseltamivir, but this was not statistically significant ($P = 0.3783$) (Table 4). Thus, no therapeutic benefit was demonstrable as a result of oseltamivir treatment in non-influenza virus-infected patients.

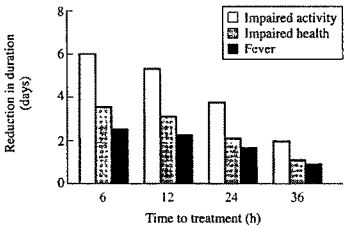

Figure 4. The median reduction in days of impaired activity and health and duration of fever with earlier treatment with oseltamivir 75 mg twice a day in comparison with delayed treatment at 48 h (intent-to-treat infected population).

Oseltamivir was well tolerated. The incidence of adverse event-related drug withdrawal was low, 25/1426 (1.8%), and was similar to the number of patients who withdrew for non-safety reasons (n = 21/1426, 1%). Most adverse events were mild or moderate in severity. The most common adverse events were gastrointestinal, mainly nausea (194/1426, 13.6%) and vomiting (160/1426, 11.2%), which resolved with continued dosing; only 12 subjects (<1%) withdrew as a consequence of these effects. The majority of these events occurred between the first and second dose (~70%). The incidence of nausea was further reduced when the first dose was taken with food (8.6%) compared with no food (13.6%, $P = 0.009$). The overall incidence of vomiting was higher in patients with influenza infection (9.9%) than in those without (6%, $P = 0.012$).

Discussion

The IMPACT study, designed to investigate the relationship of time-to-treatment with the illness duration and other efficacy parameters, has confirmed that greater and incremental benefits can be gained from treating influenza as soon as possible after the appearance of symptoms. The study design was predicated on knowledge that influenza illness is associated with virus replication in the respiratory tract that peaks 24–72 h after illness onset.[12] Thus, drugs like oseltamivir that would ameliorate illness solely by inhibiting virus replication must be administered in the first 48–72 h of illness, and preferably as early as possible. Early intervention was shown to be strongly associated with a shorter duration and a reduced severity of illness, a faster resolution of fever and a faster return to normal health and activity. For the primary endpoint, the data demonstrated that the total duration of illness could be halved if influenza patients were treated early compared with intervention at 48 h. These data complement the results from an earlier study with oseltamivir in which subjects who started active treatment within 24 h of

Table 4. Duration of illness observed in the population without laboratory-confirmed influenza (n = 461) treated with oseltamivir 75 mg twice daily for 5 days per time-to-treatment group

	Duration of illness (h) between onset of symptoms and treatment start				
	0–6 (n = 99)	>6–12 (n = 70)	>12–24 (n = 167)	>24–36 (n = 93)	>36–48 (n = 32)
Median duration (h)	83.0	77.4	112.1	124.5	196.0
(95% CI)	(75.5–107.0)	(64.8–105.3)	(97.0–133.9)	(115.5–152.0)	(133.8–250.8)

CI, confidence interval.

symptom onset had a 37% reduction in illness duration compared with 25% in those who initiated therapy within 36 h after onset of illness.[6]

This is the first report to describe the mathematical relationship between illness duration and time to effective antiviral intervention. The results based on the observed time-to-treatment group data and those produced by AFT modelling were highly comparable. The time-to-treatment group data consisted of results for all subjects recruited within specified mean 6 or 12 h windows, whereas AFT modelling permitted us to predict the effect of intervention at any time as well as the results of extrapolation to the limits of time studied. The observed effects and the values predicted by AFT modelling were somewhat different even though they were both derived from analysis of the study database.

The absence of a concurrent control group treated with placebo in this study might raise the question of whether the beneficial effects of early initiation of oseltamivir plus symptomatic therapy in persons with influenza illness were due to early initiation of symptomatic therapy alone. This is unlikely given the previous observation in persons with laboratory-confirmed influenza who were treated with the same symptomatic therapy plus placebo,[6] in whom no difference was observed in the median duration of illness between those persons treated at <36 h and those in whom therapy was initiated within 24 h of illness onset.

The study confirmed that physicians can accurately diagnose influenza in patients reporting soon after fever onset by use of a clinical case definition and knowledge that influenza virus is circulating within the community. There were no major differences in the sensitivity of the clinical diagnosis between the treatment time windows, and the 67% infection rate was similar to that found in previous placebo-controlled treatment studies with oseltamivir.[5,6] The study also confirmed that influenza presents with characteristic sudden identifiable and severe symptom onset,[13] only 2/958 patients having presented with mild symptoms in this study. Education of potential volunteers about symptoms of influenza illness made possible self-referral for diagnosis and the implementation of antiviral therapy.

The proportion of individuals with influenza who receive some form of drug treatment is 59%. Antibiotics are the most frequently prescribed drugs (45%), followed by antipyretics/analgesics (22.5%).[3] Antibiotics are likely to be prescribed to patients with influenza in all age groups.[14,15] Inappropriate antibiotic treatment provides no medical benefit and increases the risk of antibacterial resistance.[15] The results of this study confirm that oseltamivir therapy would be more logical than antibiotics for patients with uncomplicated influenza.

Translating the results of this study into clinical practice will be challenging, but, it is argued, clinically important. Strategies to do so must provide early diagnosis and access to oseltamivir therapy without markedly increasing the workload for practitioners in the influenza season. This study has demonstrated that early presentation is possible by public education of influenza symptom characteristics, as approximately two-thirds of those who were infected presented to their general practitioners within 24 h of symptom onset, and a quarter within 12 h. One solution may lie in application of the UK Department of Health guidelines to implement the NICE recommendations for another neuraminidase inhibitor drug, zanamivir.[16] Telephone triage and walk-in centres for specific patient groups organized by practice nurses or other health professionals, e.g. community pharmacists, working to a protocol of standard diagnostic questions will help address the issues of overburdened GPs and facilitate timely initiation of treatment.

The overall incidence and pattern of adverse events were similar to those reported in previous studies.[5,6] Nausea was significantly reduced by taking the first dose of oseltamivir with food, suggesting that the mechanism of action may be at the local gastric level. The proportion of patients who discontinued drug because of gastrointestinal events was small and similar to previous studies, due to the fact that the majority of these events were of isolated occurrence after the first dose and did not persist with continued dosing.

Conclusion

The IMPACT study adds to our understanding of the benefits of oral oseltamivir therapy of influenza, by demonstrating that earlier intervention enhances treatment effects. Early intervention can reduce the total illness duration by up to one

half compared with later treatment, resulting in faster recovery and resumption of normal activities. The IMPACT study demonstrated the value of early presentation, and diagnosis of patients with influenza illness and their treatment with oseltamivir.

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We thank all participating physicians, study investigators and the Roche study management team (Charlotte Harding Rains, Penny Kirkwood, Kevin Drabble, David Merritt, Laurence Bourdeau, Diane Ginn and Shelina Rajan) who made this project possible. The authors gratefully acknowledge Stephen Pawsey (clinical science), Jennifer Gilbride, Nelson Kinnersley, Tracey Mills and Paul Mahoney (biostatistics) at Roche Global Development. We would also like to acknowledge the contribution of Dr Torsten Hoof who helped with the design of this study. This study was financially supported by F. Hoffmann-La Roche Ltd.

Study investigators: Belgium: Didier, Vanret – Namur; Frans, Pardinaens – Antwerpen; Didier, Giet – Liege; Bernard, Clarysse – West-Vlaaderen; Jacques, Saintpo – Hainaut; Frank, Decoutere – Limburg; Rodolphe, Liagre – Oost-Vlaanderen; Noel, Provoost – Vlaams Brabant; Canada: Dr G. Acyuthan – Regina; Dr Marc Afilalo – Montreal; Dr Gordon Arbess – Toronto; Dr Laurie Breger – Montreal; Dr I. Campbell – Montreal; Dr David Carswell – Harrow; Dr Howard Conter – Halifax; Dr Percy Crocker– St John's; Dr Francisco Diaz-Mitoma – Ottawa; Dr Anthony D'Urzo – Toronto; Dr G.W. Hammond – Winnipeg; Dr Brian R. Holroyd, – Edmonton; Dr Allan Kelley – Edmonton; Dr Gerald Lazarenko – Calgary; Dr P.H. Orr – Winnipeg; Dr Jean-Pascal Ouellet – Sherbrooke; Dr Plyush Patel – Toronto; Dr Daniel Shu – Vancouver; Dr J.N. Simonsen – Winnipeg; Dr Guy Stiver – Montreal; Dr Sylvie Trottier – Quebec City; Dr Paul Whitsitt – Oshawa; Denmark: Bente, Klarland – Copenhagen; Ronald, Dahl – Aarhus; Jacobsen – Vig; Laybourn – Copenhagen; Schelde – Vig; Wilstrup – Soro; Pertti, Himanen – Turku; Timo, Kaitilia – Lappeenranta; Leena, Kiiski – Kuopio; Perti, Kivi – Tampere; Jamo, Koski – Jyvaskylan; Merja, Pitkanen – Helsinki; Arto, Strandberg – Helsinki; Timo, Veskiari – Tampere; France: Dr Alain Campagne – Tours; Dr Gilles Grandmottet – Besancon; Dr Michael Gregoire – Tallard; Dr Dominique Lejay – Vieux Conde; Dr Charles Mercier, Henri – Montagne; Dr Gerald Mongin – Mont Pellier; Dr Simon Musso – Eaunes; Dr Francois Spilthooren – Evreux; Dr Richard Josse – Bordeaux; Dr Bruno Pascal – Toulon; Dr Jean-Loup Rey – Armees; Dr Jean-Louis Soares – Armees; Germany: Dr Flobdorf – Duren; Dr Barghoom – Dormage; Dr Gessert – Rothenburg; Dr Schlauch – Lochham; Dr Adler – Ludwigshafen; Dr Ludke – Freiburg; Iceland: Gunnar, B. Gunnarsson – Reykjavik; Vilhjalmur, Ari Arason – Hafnarfjordur; Jon, Stiener Jonsson – Gardabaer; Ireland: Dr Tom Finnegan – Dublin; Dr Brian O'Doherty – Donaghmeade; Dr Niall Moore – Dublin; Dr Liam Lynch – Dublin; Dr Philip O'Connell – Dublin; Dr Alan Byrne – Dublin; Dr William Kavanagh – Dublin; Dr Tim Gleeson – Dublin; Israel: Prof Shai Ashkenzi – Petach-Tikva; Dr Efrat Harlev – Shoam; Prof Ethan Rubinstein – Givataeem; Dr Aya Shelem – Hedera; Dr Tessa Shelouche – Hedera; Dr Dorit Wolf – Natania; Dr Moshe Zlotnik – Ashkelon; Dr Bibiana Chazan – Tiberia; Dr Nava Gasper – Ofakim; Dr David Hassin – Hedera; Dr Nir Heilzenrat – Kiryat-Gat; Dr Doron Hemoni – Hedera; Dr Liora Ben, Nitzan Masika – Petach Tikva; Dr Raul Raz – Afula; Dr Moshe Torem – Afula; Dr Tsvika Weiss – Herzelia; Dr Yoran Menda – Herzelia; Dr Akram Abdful – Ofakim; Dr Bibiana Chazan – Tiberia; Dr Gay Nir – Afula; Dr Avraham Borer – Ofakim; Dr Bat-Sheva Gottersman – Kfar-Saba; Dr Yova Helman – Natania; Dr Oma Ofir – Afula; Prof Fransinsc Schlaeffer – Beer-Sheva A; Dr David Gabay – Rishon Lezion; Dr Oren Avraham – Natania; Dr Cama Sulliman – Tiberia; Italy: Prof Pietro Crovari – Genova; Netherlands: Dr G.J.M. Van Doesburg – Lichtenvoorde; Luiten – Den Haag; Dr R.G.G. Groot – Arnemuiden; Dr P.H.L. Hofstede – Giesbeek; Dr F.B. Naber – Heemskerk; Dr J. Veerman – Nijverdal; Norway: Sigbjorn, Elle – Elverum; Mikkel, Mundal – Oslo; Niels-Erik, Landmark – Sandvika; Sjur Rod-Larsen – Asgardstrand; Pal, Vik – Sandvika; Kristian, Furuseth – Jessheim; Sigve, Tonstad – Oslo; Aage, Bjertnaes – Trondheim; Sweden: Dr Stig Cronberg – Maimo; Dr Per Forsberg – Vaxjo ; Dr Peter Holgersson – Karlskrona; Dr Bo Claesson – Goteborg; Dr Mikael Mullart – Sundsbruk; Dr Eva Gutniak – Vaellingsby; Switzerland: Claude, Breitenstien – Liestal; Roland, Seitz – Margrethen; Urs, Beat Goflin – Binningen; Thomas, Aeschbach – Lausanne; Eric, Jensen – Bern; Blaise, Genfron – Lausanne; UK: Hall, Tim – Plymouth; Middleton – Fowey; Ritchie – Peterhead; Haworth – Blackpool; Doel – Cleveleys; Newby – Cambridgeshire; Rogers, D. – Edgbaston; Wallace, P. – Cheadle; Anderson, D. – Bristol; Crawford, A. – Winchester; Dove, N. – Harrow; Lynch, H. – Bolton; Finlay, M. – Rochdale; Gilfeather, B. – Windsor; Arora, S. B. – London; Jones, G. – Canterbury; Moseley, D. – Sheffield; Muir, W. – Nottingham; Quinn, Leslie – Glasgow; Richardson, D. – Dorset.

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Chairman TOM DAVIS. Thank you. Thank you very much.

Mr. Abercrombie.

STATEMENT OF GEORGE B. ABERCROMBIE

Mr. ABERCROMBIE. Good morning. Good morning, Mr. Chairman and members of the committee. I am George Abercrombie, president and chief executive officer of Hoffman-La Roche, a research-based pharmaceutical company. I am accompanied today by Dr. Dominick Iacuzio, our medical director for Tamiflu. I want to thank you for the opportunity to discuss the role of Roche and the antiviral drug Tamiflu in pandemic influenza preparedness and response, and I request that my full written testimony be submitted for the record.

Chairman TOM DAVIS. Without objection, everybody's full written testimony is in the record.

Mr. ABERCROMBIE. Since Roche licensed Tamiflu nearly 10 years ago, we have acted in a responsible manner, consistent with the public health role of this wonderful product and our commercial obligations. Roche remains committed to ensuring the availability of Tamiflu to patients and governments around the world, and we are optimistic that this unfortunate matter with Gilead will be resolved.

Let me now turn to the central office of this hearing, and that pandemic influenza, which is one of our greatest public health threats.

According to the Department of Homeland Security, the potential consequences of even a limited influenza pandemic could result in economic disruption, hospitalizations and deaths far in excess of most terror attacks. It is widely recognized that Tamiflu is critical and a critical tool in pandemic influenza preparedness. The Infectious Diseases Society of America has recommended that the U.S. stockpiles enough antivirals to treat up to 50 percent of the population.

Based on Roche's commitment to the product, Tamiflu is the leading prescription antiviral medication for the treatment of influenza type A and B in patients 1 year and older, and prevention of influenza type A and B in patients 13 and older. Data to support prophylactic use in children 1 year of age and older were recently submitted to FDA for review.

The efficacy of Tamiflu against avian influenza has been demonstrated by leading researchers and animal studies and in vitro data, and is supported by practical experience during a 2003 avian influenza outbreak in the Netherlands. In contrast to an antiviral drug requiring inhalation, orally ingested Tamiflu has been shown to be systemically active in humans. This is important because evidence derived from infected humans and animals suggests significant systemic involvement of the H5N1 avian virus.

Although the potential for resistance must be monitored carefully, no transmission of a Tamiflu-resistant virus in humans has been detected to date. Accordingly, the World Health Organization has recommended the use of Tamiflu to help control the avian flu outbreaks in Asia.

Roche continues to work closely with public health officials, physicians, and other healthcare professionals around the world in a

manner that is responsible and complimentary to seasonal flu vaccination programs. We have recommended against, and do not advocate for, indiscriminate uses which could lead to resistance, such as the prophylactic veterinary use of amantadine, recently reported in Asia.

Given inherent complexities in Tamiflu production, surge capacity to meet immediate, large-scale demand upon the outbreak of a pandemic, simply does not and cannot exist. The manufacturing process for Tamiflu takes 8 to 12 months from raw materials to finished product. The process involves many inputs and steps, including a unique starting material and a potentially explosive production step that can be carried out only in specialized and very costly facilities. Despite these limitations, since 2003, we are increasing total Tamiflu production capacity nearly eight-fold.

At the request of the U.S. Government, Roche has developed a new U.S.-based supply chain that will be launched in the third quarter of this year. Further, we have developed special U.S. packaging for stockpiled Tamiflu to extend the shelf life and ease distribution and administration. In addition, Roche has also discovered and developed a synthetic process for manufacturing the chemical used in the initial production step. This will ultimately reduce reliance on natural sources.

Roche has received and is filling on schedule pandemic stockpile orders for Tamiflu from 25 countries, and we have received letters of intent from five additional governments. Countries such as the United Kingdom, France, Finland, Norway, Switzerland, and New Zealand are ordering enough Tamiflu to cover between 20 and 40 percent of their populations. And just this morning the country of Portugal announced an order for 25 percent of their population.

Although discussions are underway with the U.S. Government to purchase significantly greater amounts of Tamiflu, achieving domestic stockpile levels comparable to other nations will require firm, sustained commitments from the U.S. Government.

If I can leave you with three messages, they are the following: first, there is a consensus by global health authorities that Tamiflu is an important tool in pandemic influenza preparedness and response; second, other nations are currently well ahead of the United States in Tamiflu stockpiling. We urge the United States to make expanded commitments now and over time to ensure an adequate Tamiflu stockpile.

Finally, I want you to know, Mr. Chairman and this committee, that the availability of Tamiflu as a part of a robust pandemic response remains my top priority as chief executive officer of Hoffman-La Roche.

On behalf of Roche, thank you for highlighting this critical public health issue. And Dr. Iacuzio and I will be pleased to answer any questions you may have.

[The prepared statement of Mr. Abercrombie follows:]

STATEMENT OF GEORGE B. ABERCROMBIE
PRESIDENT AND CHIEF EXECUTIVE OFFICER, HOFFMANN-LA ROCHE INC

BEFORE THE
COMMITTEE ON GOVERNMENT REFORM
UNITED STATES HOUSE OF REPRESENTATIVES

THE NEXT FLU PANDEMIC: EVALUATING U.S. READINESS

JUNE 30, 2005

Mr. Chairman and Members of the Committee, I am George Abercrombie, President and Chief Executive Officer at Hoffmann-La Roche Inc. ("Roche"), a research-based pharmaceutical company. I am grateful for this opportunity to discuss with you the roles of Roche and antiviral drugs in pandemic influenza preparedness and response, and I commend the Committee for its efforts to protect the American people against this very real public health threat.

THE PANDEMIC INFLUENZA THREAT

Every year, seasonal influenza causes an average of 36,000 deaths and 200,000 hospitalizations.[1] In addition to the annual influenza seasons, three influenza pandemics took place during the 20th century. In 1918, approximately 500,000 people in the United States died from the so-called "Spanish Flu," and up to 50 million may have died worldwide. The 1957-58 "Asian flu" killed 70,000 Americans, and the 1968-69 "Hong Kong flu" caused over 34,000 deaths in this country.[2]

An influenza pandemic occurs when an existing influenza strain mutates. The emergence of such a new viral strain, the lack of previous exposure and immunity to the virus, and the lack of a

[1] William W. Thompson et al., *Influenza-Associated Hospitalizations in the United States*, 292 JAMA 1333 (2004).

[2] Centers for Disease Control and Prevention, *Fact Sheet: Information About Influenza Pandemics* (March 8, 2005).

vaccine that can protect against the new strain can ignite a global influenza epidemic, *i.e.*, a pandemic.

It now appears that the factors associated with a pandemic are moving into place. First, we have a highly pathogenic strain of avian influenza circulating widely in Asia. Second, this avian strain appears to be increasingly capable of causing deadly disease in humans and animals. In fact, the avian virus has been fatal in approximately 50 percent of people infected by it.[3] While efficient human-to-human transmission of the virus – the critical barrier to an influenza pandemic – has yet to occur, it is possible – if not probable – that persons harboring both human and avian influenza viruses could become "mixing vessels" from which a new virus emerges that is easily transmitted among humans. Indeed, a recent World Health Organization (WHO) assessment noted that new epidemiological findings in Asia indicate that the virus may be becoming more capable of human-to-human transmission.[4]

Make no mistake: should an influenza pandemic occur, the threat to the U.S. public would be great. In its draft *Pandemic Influenza Preparedness and Response Plan* (Plan), the U.S. Department of Health and Human Services (HHS) recognizes an influenza pandemic as having "a greater potential to cause rapid increases in death and illness than virtually any other natural health threat."[5] Health experts estimate that if the virus is passed efficiently between humans, avian flu could result in a pandemic causing over 50 million deaths worldwide.[6] Studies cited recently by the Centers for

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[3] World Health Organization, *Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO* (June 17, 2005), *available at* http://www.who.int/csr/disease/avian_influenza/country/cases_table_2005_06_17/en/print.html.

[4] World Health Organization, *Inter-country Consultation, Influenza A/H5N1 in Humans in Asia* (May 6-7, 2005).

[5] Department of Health and Human Services, *Draft Pandemic Influenza Response and Preparedness Plan, Executive Summary* 3, (Aug. 2004), *available at* http://www.hhs.gov/nvpo/pandemicplan.

[6] World Health Organization, *Estimating the Impact of the Next Influenza Pandemic: Enhancing Preparedness* (Dec. 8, 2004), *available at* http://www.who.int/csr/disease/influenza/preparedness2004_12_08/en/index.html.

Disease Control and Prevention (CDC) estimate that, without vaccines or drugs, a "medium level" pandemic would kill between 89,000 and 207,000 Americans, and sicken another 20 to 47 million – causing up to 42 million outpatient visits and 734,000 hospitalizations.[7] In fact, according to the Department of Homeland Security, the potential consequences of even a limited influenza pandemic could result in deaths, hospitalizations and economic disruption far in excess of most terror attack scenarios.[8] In addition to the human toll, the economic cost of such a pandemic has been estimated at $71 to $167 billion.[9] Without a doubt, planning for such a global health crisis must be a major public health priority.

Both the HHS draft Plan and the WHO *Global Influenza Preparedness Plan* emphasize that adequately addressing the threat of a pandemic influenza outbreak will require availability of both an influenza vaccine and antiviral drugs.[10] If available, vaccines, which typically are administered before an outbreak of influenza, can provide an effective defense against developing seasonal or pandemic influenza, as well as in slowing transmission among humans.

In our seasonal marketing of Tamiflu®, we have carefully calibrated our messages and activities so they are complementary to, and do not undermine, efforts to promote broad seasonal vaccination for influenza. However, vaccines have important limitations, particularly in the pandemic influenza context. First, accurately predicting the specific viral strain or strains that ultimately may cause an influenza pandemic cannot be assured. Consequently, effective vaccines

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[7] Centers for Disease Control and Prevention, *Influenza Pandemic Fact Sheet* (Mar. 8, 2005), *available at* http://www.cdc.gov/flu/avian/gen-info/pandemics.htm.

[8] *15 Nightmares for Disaster Planning*, N.Y. Times (March 16, 2005).

[9] CDC, *Influenza Pandemic Fact Sheet.*

[10] Department of Health and Human Services, *Draft Pandemic Influenza Response and Preparedness Plan, Core Document* 23 (Aug. 2004), *available at* http://www.hhs.gov/nvpo/pandemicplan/finalpandemiccore.pdf; World Health Organization, *WHO Global Influenza Preparedness Plan* 13 (2005), *available at* http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_2005_5.pdf.

may not be available at the time a pandemic outbreak is first detected. Second, the propensity of viruses to mutate can lead to the rapid generation of new strains. Thus, there is a possibility that a vaccine effective against the viral strain accountable for the outbreak may be impotent against the virus' mutated progeny. This is one reason why unique vaccines to guard against seasonal influenza must be produced, licensed, and distributed each year, and thus, cannot be stockpiled for use against multiple outbreaks. Finally, given the pace of an outbreak of pandemic influenza, initial reliance on vaccines may not be feasible. For example, the WHO estimates it will take six to nine months to develop a vaccine effective against the circulating pandemic virus strain.[11] Of course, producing and distributing the vaccine on a large scale also will take considerable time, and a vaccine, once administered, may take several weeks to trigger immunity, or require multiple administrations.

For all of these reasons, HHS and WHO have recommended that efforts to prepare for an influenza pandemic not rely on vaccines alone. As stated in a recent WHO report, "pending the availability of vaccines, antiviral agents will be the principal medical intervention for reducing morbidity and mortality, which becomes the most important priority once a pandemic is underway."[12] Notably, certain antiviral drugs can be used either to treat the flu or as a prophylactic to prevent those at risk from becoming infected. Recently published models suggest that an influenza pandemic could be contained if 80 percent of those exposed to the virus used targeted antiviral drugs prophylactically.[13]

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[11] World Health Organization (WHO) Global Influenza Preparedness Plan: The Role of WHO and Recommendations for National Measures Before and During Pandemics (Apr. 2005), *available at* http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_EDC_99_1/en/print.html.

[12] World Health Organization, *Avian Influenza: Assessing the Pandemic Threat* (Jan. 2005), *available at* http://www.who.int/csr/disease/influenza/H5N1-9reduit.pdf.

[13] N.M. Ferguson et al., *A Population-Dynamic Model for Evaluating the Potential Spread of Drug-Resistant Influenza Virus Infections During Community-Based Use of Antivirals*, 51 Journal of Antimicrobial Chemotherapy 977 (2003); I.M. Longini et al., *Containing Pandemic Influenza with Antiviral Agents*, 159 Am. J. Epidemiology 623 (2004).

Finally, antivirals have four additional characteristics that warrant their inclusion in any influenza pandemic plan: (1) antivirals have a long shelf-life – five years in the case of Tamiflu® capsules – permitting them to be stockpiled and immediately available when an outbreak occurs; (2) antiviral drugs begin to work immediately after they are administered; (3) certain antivirals work against multiple types of influenza; and (4) utilization of antivirals does not interfere with immunologic response, meaning that patients can still develop immunity to the virus while taking Tamiflu® to protect them.

THE ROLE OF TAMIFLU® IN AN INFLUENZA PANDEMIC

Roche's Tamiflu® (oseltamivir phosphate) is the leading prescription oral antiviral drug for influenza. Roche licensed the product from Gilead Sciences, and accelerated development of the product through Phase II and III studies, as well as the Food and Drug Administration (FDA) approval process. Recently, Gilead Sciences sent to Roche a notice seeking to revoke the license for Tamiflu®. We at Roche are deeply disappointed by Gilead's actions, and strongly disagree with their public statements regarding Roche's Tamiflu®-related efforts. However, we are also optimistic that the dispute will be resolved, and committed to ensuring this matter does not disrupt or delay the production and subsequent availability of Tamiflu®, or impinge upon supply commitments made to governments around the world.

Tamiflu® was first approved by the FDA in 1999 for the treatment of adults with type A and B influenza. Specifically, Tamiflu®, a neuraminidase inhibitor, works by attacking the influenza virus and its ability to replicate, rather than simply addressing influenza symptoms. Currently, Tamiflu® is indicated for treatment of patients one year and older, and, if taken within forty-eight hours of the onset of symptoms, can help patients feel better faster. As a prophylactic, an indication approved in 2000, Tamiflu® is labeled for use by adults and adolescents 13 years of age and older, although data on children one year of age and older have recently been submitted to FDA for

review. Tamiflu® has a low likelihood of clinically significant drug interactions and is generally well-tolerated, with nausea and vomiting being the most frequently reported adverse events. Tamiflu® is available in both capsule and oral suspension form.

In congressional testimony delivered last month, CDC Director Dr. Julie Gerberding reaffirmed that Tamiflu® "is the only antiviral at this time shown to be effective against the H5N1 avian influenza virus in Asia."[14] The efficacy of Tamiflu® against avian influenza has been demonstrated in animal studies by leading researchers, *in vitro* data, and practical experience during an avian influenza outbreak in the Netherlands.[15] Further, evidence derived from infected humans and animals suggests significant systemic involvement of the H5N1 avian virus. Importantly, in contrast to an antiviral drug requiring inhalation, orally ingested Tamiflu® has been shown to be systemically active in humans. Accordingly, the WHO has recommended use of Tamiflu® in those potentially exposed to avian flu in Asia.[16]

Recent news reports have highlighted the resistance to the antiviral drug amantadine due to veterinary use of the drug in China. To the best of our knowledge, no comparable veterinary use has occurred with respect to Tamiflu®, and we certainly do not advocate such use. While a possibility exists for an influenza virus to emerge with decreased sensitivity to any antiviral drug, the Tamiflu®-resistant viruses isolated in humans to date do not appear to be effectively transmissible.[17]

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[14] *The Threat of and Planning for Pandemic Flu: Hearing Before the Subcomm. on Health of the House Comm. on Energy & Commerce* 109th Cong. (May. 26, 2005) (Statement of Dr. Julie Gerberding).

[15] I.A. Leneva et al., *The Neuraminidase Inhibitor GS4104 (Oseltamivir Phosphate) is Efficacious Against A/Hong Kong/156/97 (H5N1) and A/Hong Kong/1074/99 (H9N2) Influenza Viruses*, 48 Antiviral Res 101 (2000).

[16] World Health Organization, *WHO Interim Guidelines for Health Monitoring of Persons Involved in Culling of Animals Potentially Infected with Highly Pathogenic Avian Influenza Viruses* (Mar. 22, 2004), *available at* http://www.wpro.who.int/avian_flu/docs/Health_monitor_person.asp.

[17] Data collected from patients treated with Tamiflu®, at its approved dose and for the approved treatment duration, demonstrate an overall incidence of resistant virus of only 0.4 percent in adults and four percent in children aged one to 12. All of the resistant virus strains were found unlikely to spread within a community, even under conditions of widespread Tamiflu® use for both treatment and prevention of influenza. N. Roberts, *Treatment of Influenza with Neuraminidase Inhibitors: Virological Implications*, 356 Philosophical Transactions of the Royal Society 1895 (2001).

Population sampling also indicates that resistance to Tamiflu® is very infrequent. To ensure Tamiflu® remains effective against the influenza virus, Roche does not recommend strategies which may utilize lower doses or shorter duration of therapy compared with the recommended dose.

For the prevention of influenza in those 13 years or older, Tamiflu® can be administered once a day for at least 7 days following close contact with an infected individual who demonstrates characteristic symptoms of influenza. Tamiflu® can also be taken for up to 6 weeks for seasonal prophylaxis if influenza is circulating in the community. However, the approved dose for the treatment of influenza – 75mg twice daily for five days – is expected to represent the minimum required for the management of an influenza pandemic.

If integrated into a strong pandemic preparedness and response plan, Tamiflu® could be critical both as a stopgap intervention pending the availability of a vaccine, and to treat or prevent further infections once a vaccine is available. During a pandemic, there will be heightened awareness of influenza and – with a functioning infrastructure and appropriate prepositioning – rapid treatment can be achieved.

ALTHOUGH ROCHE IS TAKING STEPS TO INCREASE TAMIFLU® PRODUCTION, THE U.S. GOVERNMENT MUST MAKE CONTRACTUAL STOCKPILE COMMITMENTS TO ENSURE A ROBUST U.S. ANTIVIRAL DRUG SUPPLY

As noted, both HHS and the WHO include stockpiling of antiviral drugs as a central component of their developing plans for influenza pandemic preparedness. The Infectious Diseases Society of America (IDSA) and the WHO have recently acknowledged that Tamiflu®, in particular, is uniquely suited to pandemic stockpiling, for several reasons: (1) its efficacy against influenza types A and B; (2) the absence of a known Tamiflu®-resistant virus transmissible in humans; (3) the product's five-year shelf life; and (4) its capsule formulation.

It is imperative that Tamiflu® be stockpiled in advance of the outbreak of a pandemic because inherent complexities in production severely limit capacity to rapidly meet large-scale demand arising once a pandemic occurs. The manufacturing process for Tamiflu® is complex, and takes 8-12 months from raw materials to finished product. The process involves many intermediate steps, including a unique starting material, and a potentially explosive production step that can be carried out only in specialized and costly facilities. Given these complexities, significant lead time is needed to increase production capacity and build stockpiles of the quantity required for an influenza pandemic. The historical commercial, seasonal market for Tamiflu® has been modest in relation to pandemic stockpiling needs and would quickly be depleted in the event of a pandemic.

Historically, Roche has produced enough Tamiflu® to meet the seasonal influenza demand. We have worked diligently to educate health care professionals and patients on the appropriate use of Tamiflu®, seeking to expand the seasonal market while not undermining public health messaging regarding vaccinations. This educational process has resulted in steady growth in Tamiflu® prescriptions in the United States in recent years, from roughly 700,000 in the 1999-2000 flu season to over 1.7 million in the most recent flu season. In contrast, the IDSA recommends that the government stockpile enough antiviral drugs to treat up to 50 percent of the U.S. population, or almost 150 million patients.

Roche has been proactive in recognizing and responding to public health needs. For example:

- To achieve levels of production needed for stockpiling, Roche doubled production capacity at our European facility from 2003 to 2004, and we are doing so again during 2005. Roche plans additional expansion of production capacity for Tamiflu® in 2006.

- We have also built a U.S.-based supply chain that, when launched later this year, will result in an increase in total global Tamiflu® active pharmaceutical ingredient and capsule production capacity of nearly eight-fold over production capacity in 2003.
- Roche developed special U.S. packaging for stockpiled Tamiflu® in order to extend dating and ease distribution and administration.
- We discovered and developed a synthetic process for manufacturing the chemical used in the initial production step, which will ultimately greatly reduce reliance on natural sources.
- Roche has also been working with the WHO, providing supplies of Tamiflu® for the avian flu outbreaks to date. We are now working with WHO to establish a rapid response stockpile in an attempt to slow or halt the virus at its origin.

Roche has received and will fill – on schedule – pandemic stockpile orders and letters of intent for Tamiflu® from 30 countries worldwide. In fact, countries such as the United Kingdom, France, Finland, Norway, Switzerland and New Zealand are ordering enough Tamiflu® to cover between 20 to 40 percent of their populations. In contrast, HHS stockpile purchases to date total approximately 2.3 million courses of treatment – or enough to treat less than one percent of the U.S. population. We are in discussions with the U.S. government regarding an expanded commitment to procure supplies of Tamiflu® for the national stockpile. Based on such commitments, and as we have done to date, Roche is more than willing to work with HHS to further increase capacity in order to build a robust national stockpile.

Alerted to the pandemic threat, governments now have an unprecedented opportunity to attempt to minimize the catastrophic loss of life, debilitating illness, and enormous economic costs that a pandemic could wreak on the United States and the world. If I can leave you with three messages from my testimony today, they are the following. First, there is a consensus by global health authorities that Tamiflu® is an important tool in pandemic influenza preparedness and

response. Second, other nations are currently well ahead of the United States in Tamiflu® stockpiling, and we urge the U.S. to make commitments now – and sustain these purchases over time – to ensure an adequate stockpile. Finally, I want you to know that the availability of Tamiflu® as part of a robust pandemic response remains my top priority as Chief Executive Officer of Hoffmann-La Roche.

We at Roche want to continue to work closely with this Committee, HHS, and governments around the world to assist in ensuring our pandemic preparedness. On behalf of Roche, thank you for highlighting the importance of this critical public health issue. Dr. Iacuzio and I will be pleased to answer any questions you may have.

Chairman TOM DAVIS. Well, I thank all of you for your testimony. As I noted, your entire testimony is in the record, and questions will be based on that. Let me start off.

Dr. Milligan, let me start with you. In your opinion, has the United States stockpiled a sufficient amount of Tamiflu to prepare against the threat of a flu pandemic?

Dr. MILLIGAN. If you compare the United States to governments around the world, it is woefully inadequate and way below the levels that would be recommended by not only U.S. health authorities, but by world health authorities. So I believe it is far too low.

Chairman TOM DAVIS. If something were to occur here, how quickly could we be able to get this out to the population? If the United States were to come in and order millions of more doses tomorrow, how quickly would it be before they could receive it? I will ask either you or Mr. Abercrombie, if there is a consensus there.

Mr. ABERCROMBIE. Well, as I stated, Mr. Chairman, it takes 8 to 12 months to manufacture Tamiflu. It is a very complex multi-step process involving, at one step, potentially explosive material. We have done everything we can to accelerate that process; we have increased production capacity eight-fold. So we cannot rely on the ability to flip a switch and suddenly make large quantities in the event that a pandemic breaks out. That is why it is crucial to stockpile large quantities well in advance of a pandemic.

Chairman TOM DAVIS. Do you agree with that, Dr. Milligan?

Dr. MILLIGAN. I actually disagree with that, because you can in fact stockpile large amounts of the active pharmaceutical ingredient. So you can stockpile significant amounts, and this stores virtually indefinitely at refrigerated conditions.

Chairman TOM DAVIS. So the ingredients you can store separately?

Dr. MILLIGAN. The ingredients you can store. The rate-limiting step, then, becomes the capsuling process. And that would require significant orders from governments in order to fill those, because once you make a capsule, it starts to expire.

Chairman TOM DAVIS. How long does it take to capsulize it, is that pretty quick?

Dr. MILLIGAN. Depends on how many production lines you have and your commitment to that. Making an individual capsule is very fast, but making tens of millions or hundreds of millions would require multiple production lines.

Chairman TOM DAVIS. Yes, Mr. Abercrombie.

Mr. ABERCROMBIE. If I can just respond to that. In fact, we do store large quantities of the raw materials, predominantly here in the United States, because the United States is the primary site of moving those materials into finished product. And even by storing large materials, it is about a 6-month process before you can, from that point, have finished material on the marketplace.

Chairman TOM DAVIS. The shelf life is what, at least 5 years?

Mr. ABERCROMBIE. The approved shelf life is currently 5 years. We have worked with the Government to extend the shelf life. The Government is working with the strategic national stockpile to determine if that can be extended in the event of a security problem with a pandemic.

Chairman TOM DAVIS. You heard our first panel basically say that we need to have more of this. This is the stopgap until you develop your vaccine. OK.

Dr. Crosse, the GAO has previously reported that regional planning between States is inadequate to respond to bioterrorist attacks. The response to an infectious disease such as influenza is very similar to bioterrorism. Did we see effective regional cooperation and information sharing during the flu vaccine shortage last fall?

Dr. CROSSE. We saw some. I think that there are some established networks that were already in place. I think that has increased. Last year, however, it was primarily something that was centralized with CDC, so there was much greater centralized control of the distribution once the shortage was identified. I think that we did see some cooperation. Minnesota already heads a multi-State purchasing cooperative for the purchase of influenza vaccine, so that is some regional cooperation that already exists. Dr. Selecky talked a little bit about some regional activities in the Northwest. But it is not something that is true in every part of this country.

Chairman TOM DAVIS. What States were most successful in dealing with last season's flu vaccine shortage?

Dr. CROSSE. Well, in part it was States that had ordered from Santa Fe, and so they were fortunate in that their supplies were not as limited. But also it was States, I think, who had done more prior planning.

In particular, we saw success in Minnesota, which had an adequate supply and, in fact, had enough vaccine that they were able to offer vaccine to other States. California had a pretty high success rate in reaching populations. Some other States, though, had much more difficulty. Both Maine and Florida, among the States that we visited, had a lot of difficulty in covering their high-risk populations and did not have the same sort of vaccination rates that they had hoped to achieve.

Chairman TOM DAVIS. Dr. Selecky, during last year's flu vaccine shortage, some States ended up having adequate supplies of vaccine to meet the demand from high-risk groups, and were even able to offer vaccine to some lower risk. Other States couldn't even meet the demands of the high-risk groups. Now, Chiron has recently announced that their production rates may be short again this year. Better than last year's, but be short of what they had hoped.

Does ASTHO have recommendations about how distribution among the States might be more evenly achieved?

Ms. SELECKY. Actually, ASTHO would recommend that Centers for Disease Control and the Federal Government bring us into the discussions as quickly as they know that there could be a shortage. Last year I think we were all caught off guard on October 5th, when we learned that we lost one of our manufacturers. And we weren't quite ready to address the question that was immediate from the public: Where can I get mine today? Will it come to my community?

When we did engage with the Centers for Disease Control, who needed to work with the private manufacturers, I think that is one of the issues that we face in this country; we have a private supply,

a privately delivered product, but a public demand and a public need. And I think that is what is certainly behind the ASTHO recommendation that we need a national adult immunization policy in this country; we need to have incentives, as we mentioned before, for vaccine manufacturing.

The States are ready to move into that action. Guidance from the Federal Government is essential. A common message to the public is very important. But particularly for those of us at States, we had a sub-rosa network that was about finding out who needed, who had, how we could get it across lines, as it were, because we don't control the sales, either, to release from our States. In the Northwest we paid attention to what recommendations by what age that we would be giving the vaccine, so that we didn't confuse our public who hears the same media.

There is clearly work to be done, and I would suggest that the Centers for Disease Control start working with us now about that potential.

Chairman TOM DAVIS. Thank you. Thank you very much.

Mr. Burton.

Mr. BURTON. Thank you, Mr. Chairman.

Mr. Abercrombie, do they produce Tamiflu in Indianapolis? Is that your plant that you do production of that?

Mr. ABERCROMBIE. No, sir. The Indianapolis plant is from our Diagnostics Division. We have Tamiflu production scattered across other States in the United States, including New Jersey, South Carolina, North Carolina, California, and Boulder, CO.

Mr. BURTON. OK. Your headquarters is there, though.

Mr. ABERCROMBIE. Headquarters for the Diagnostics Division is in Indianapolis.

Mr. BURTON. Is that where you are located?

Mr. ABERCROMBIE. I am located in Nutley, NJ. Pharmaceutical Division is different from the Diagnostics Division.

Mr. BURTON. You need to move to Indiana; it is a great State.

Mr. ABERCROMBIE. I visit there often.

Mr. BURTON. Good.

I think Mr. Milligan indicated—and I understand you guys have a little difference of opinion right now—that you could open up more production lines in order to speed up the production and get more on the shelf quicker. Because the possibility of a pandemic does exist, have you considered that, or is your company considering opening up more production lines to meet the potential demand for this?

Mr. ABERCROMBIE. Yes, sir. In fact, since 2003 we have increased the global production capacity eight-fold. We continue to work 24/7 to do so. At the request of the Department of Health and Human Services, we have building, have completed a supply chain dedicated right here on U.S. soil that we expect approval from the FDA in the third quarter.

The real issue, sir, is not capacity from a U.S. perspective; it is we need firm orders. We are fulfilling orders around the world on a first come, first serve basis, and the United States is woefully behind the other countries I mentioned in my testimony in providing orders. But the answer is we will provide whatever capacity is nec-

essary to meet global demand for a pandemic. We have and will continue to do so.

Mr. BURTON. Let me make sure I have this straight. You could probably meet the demand that is necessary to protect a large segment of the American population if our health agencies gave you the order to go ahead and produce the product.

Mr. ABERCROMBIE. If we had received a substantial order merely a year ago, sir, we could have delivered tens of millions of courses of therapy this year. Unfortunately, other countries have gotten in line ahead of the United States.

Mr. BURTON. Have our health agencies given you any reason why they have not placed the orders?

Mr. ABERCROMBIE. I can tell you, sir, that me, personally, and other people from Roche have met with senior officials at HHS, CDC, other Members of Congress, and they all agree we need a stockpile, as you heard from the first panel. But I cannot answer why the large order commitment has not yet come.

Mr. BURTON. Mr. Chairman, I would suggest that maybe it would be a good idea for you and the vice chairman and myself and others to sign a letter to our health agencies, HHS, and ask them why they haven't put in a request or an order for an adequate supply of this. If the risk is as great as it appears to be, and it is uncertain as to when this problem might occur, it seems to me that we ought to be prepared for it. And I would like to join with you, if you see fit, to send a letter of inquiry over there.

Chairman TOM DAVIS. Well, I think we will do that. With a 5-year shelf life, I just think that it makes a lot of sense. And if you heard from the first panel as well, from Federal experts, they seem to agree with that, Mr. Burton. So we will try to do that.

Mr. BURTON. I would be happy to join you in that, Mr. Chairman.

Chairman TOM DAVIS. That would be great.

Dr. Iacuzio.

Dr. IACUZIO. Excuse me. I just wanted to add right now we have FDA approved 5-year shelf life. But there is all indication by our chemists that the product is stable longer. And with this shelf life extension program, it could go beyond.

Chairman TOM DAVIS. And it can be used for other strains of flu.

Dr. IACUZIO. Yes.

Chairman TOM DAVIS. Like for last year we could have used this.

Mr. BURTON. Mr. Chairman, I have no more questions. I just think that would be a little stimulus to our health agencies to get on the ball and make sure that we place the order so we will be adequately protected. Thank you, Mr. Chairman.

Chairman TOM DAVIS. Thank you very much.

Mr. Shays.

Mr. SHAYS. Thank you.

Dr. Crosse, it is a bit reassuring that other States have further developed important aspects of public health preparedness. However, it is a concern to know that we still have a lot of work left. And I am not clear as to where the areas of work are.

Dr. CROSSE. I think there are a number of areas of work. One of the ones we highlighted today is in planning to deal with any large-scale infectious disease outbreak, be it pandemic influenza or

any other emerging infectious disease in terms of the hospital capacity and the healthcare work force capacity. This is something that there has been a stream of Federal funding to assist in that effort, but it is still not adequate to deal with a kind of pandemic situation where we believe that hospitals would be overwhelmed.

The other efforts that have benefited from some funding from the Federal Government are in planning for infectious disease outbreaks. There has been some planning at the local level on how to run mass immunization campaigns, but we realized this past winter that there are still many locations that were not set up or not staffed, or had not yet determined how they could run through the public health department a mass immunization effort. That was something that was supposed to have been worked out when they were working on small pox vaccination campaign, but we realized that there are still communities where this is a major challenge.

Mr. SHAYS. Ms. Selecky, has the dissemination of critical information during previous flu seasons to State and local government officials and health institutions been adequate, and how could it be improved?

Ms. SELECKY. The Centers for Disease Control is just completing a round of regional meetings with all of us in the States to learn the lessons from the past and to prepare in better ways for the future. So work continues to be done on that. There is always something new to learn, and whether it is our State plan, it needs to be exercised and then revised.

And to pick up on a point made by Dr. Crosse, in the tri-cities area, where Hanford is, actually, the local health department was the only provider of flu vaccine in the community, in 3 days gave out the 10,000 doses they were lucky to have, on October 7th, 8th, and 9th, using mass vaccination and the plans that we had for any kind of mass vaccination. The State of Arkansas did much the same.

We continue to learn from those, but as I expressed in my testimony, we are quite concerned that we get additional priorities placed on us for use of the cooperative agreement for preparedness, including the pandemic flu planning at, though, an Administrative decision for a reduction. Clearly, the pandemic flu planning is absolutely essential for the protection of our general public.

Mr. SHAYS. I am not quite clear what kind of guidance is being provided by the Federal agencies and to State and local officials to help prepare them to handle a significant outbreak. So let me ask you this. How has the Federal Government supplemented your response efforts in handling the various public health threats that have surfaced in your jurisdiction?

Ms. SELECKY. Clearly, the work that has been done around the strategic national stockpile is work that is new over the last several years of public health preparedness, and particularly with all the emphases since 2001. So the fact that there is stockpiling going on, the number of stockpiles available to the Nation have increased, the practice that we do with our Federal partners on that distribution is additional help.

We are all waiting for the next draft of the Federal pandemic flu plan so that we can revise our State plans as appropriate. But States have not sat back and just waited for that to come out. So

that is one where there is a pull me, push me relationship going on, clearly.

The work that is done with our epidemiologists in our laboratories, being able to do surveillance and identify flu, has definitely increased. However, we continue to be at the mercy of what is in the stockpile, what is purchased, and that is clearly a Federal asset and not a State or local asset.

Mr. SHAYS. Thank you.

Dr. Hearne, we have heard that some States are experiencing a shortage of trained public health specialists and epidemiologists. How serious is this crisis? First, is it a crisis? And, if so, how serious is it? And what steps can and should be taken to improve training for healthcare workers?

Dr. HEARNE. Across the board we have found—whether it is epidemiologists, lab scientists, even some of the critical environmental scientists who would respond in a chemical bioterrorist event—there are huge work force shortages. It is perhaps one of the greatest problems facing our public health systems from State to State. A report that we put out last year, "Ready or Not," identified those gaps and identified some of the recommendations to go forward with this.

I think it is an area that must be significantly addressed, particularly as we are talking about beefing up the stockpile, getting supplies. You need to have those front line forces who would do the distribution of those materials, or rapidly identify an outbreak and hopefully contain it before you even need those materials. That is, first and foremost, job No. 1 that we need to focus on with public health.

Mr. SHAYS. Let me ask you has vaccination as a primary strategy for protecting individuals who are at greatest risk contributed to the lack of antiviral production capacity in the United States?

Dr. HEARNE. With antiviral or vaccine? I am sorry.

Mr. SHAYS. Antiviral.

Dr. HEARNE. One of the issues is—as we have been looking at just stockpiling—this is a very new effort that has been ramped up in just recent years since September 11th. We have recognized that we have critical materials missing. Antivirals have not been the top priority, but it is now bouncing up to the top as we are starting to recognize the seriousness and potential severity of a pandemic.

Mr. SHAYS. So the question, though, as we are looking to protect the folks at the greatest risk, has that impacted our supply?

And I will allow others to respond.

In other words, we don't stockpile it, we are out there using it in anticipation because they are at risk, correct?

Dr. HEARNE. Well, one of the lessons we learned from the previous shortage in the flu vaccine is that we didn't have those distribution systems in place. We had challenges of identifying who was even most at high-risk, how to get them out there, and how to assure that. This is, again, a balancing act of making sure that we are creating sufficient demand for materials so that we can have either ready-to-use materials and also stockpiles, and the distribution mechanisms to effectively reach those most at need.

Mr. SHAYS. The staff would like this question asked of Roche. The CDC conducts a strong flu vaccine campaign in the early fall

of every year. Does Roche actively market Tamiflu during this time? How does Roche's marketing strategy compliment CDC's strong immunization method? And do you believe that heavier marketing by Roche during the annual flu season could have increased demand and production capabilities for Tamiflu over the years?

Mr. ABERCROMBIE. Since launching Tamiflu, we have acted responsibly to ensure that we convey to physicians the role of both vaccines and Tamiflu. We encourage that all patients who need to be vaccinated be vaccinated. There is clearly a role for vaccines. And then there is a role for Tamiflu, in case you are infected with influenza. We usually, including last season, actually disseminate the CDC guidelines so that we are very transparent and up-front with that. We do not want to indiscriminately advocate Tamiflu use, we want to make sure it is used consistent with the guidelines. And there is a role for both in normal influenza, as well as a pandemic.

Mr. SHAYS. Let me ask is there any question that you all want to put on the record? In other words, do you want to ask yourself a question that you can then answer to put on the record? Is there anything that the record would be incomplete without that answer being asked? It is a serious question to ask, it is usually my best question.

Yes, Ms. Selecky.

Ms. SELECKY. I would have you ask me the question as to what intervention States are prepared to take should we be faced with pandemic flu.

Mr. SHAYS. That is a great question. Why don't you answer it?

Ms. SELECKY. And, if so, I think what we have to do is absolutely look at it as a comprehensive approach. Yes, antivirals are important. Yes, vaccine and routine every-year vaccine is essential. But we must be able to do the enhanced disease surveillance. I recently was at a global health summit in the Pacific Northwest with 16 countries from the Pacific Rim who were represented, including those countries that have avian influenza in human populations. The head of the World Health Organization and all of the leading medical and governmental folks from those countries said you must have public health infrastructure in place if we are going to even think about addressing a pandemic of the proportion we are all concerned about.

So it is about surveillance, it is about your State and local public health system. It is also about community containment strategies, making sure we use things like quarantine and isolation appropriately, or simple things like cover your mouth or stay home, those basic public health things.

A third would be antivirals; a fourth would be vaccine; and clearly the issue of healthcare system surge planning. We must be at the table with our hospital partners. We must understand that we may stop certain activities if we were ever hit with a pandemic. But we have all got to deal with—every one of us, State, Federal, local—good and important risk communication. The public expects to tell them what they know in a way that they can figure out how to protect themselves and their families.

Thank you.

Mr. SHAYS. Thank you. Thank you for that question and thank you for that answer.

Is there any other question that you need to ask yourselves here? Anyone else want to put anything else in the record?

[No response.]

Mr. SHAYS. Well, let me just thank you. Let me just ask this last question. What country does this the best, protects the public the best? Who would be the best model around the world? And if you choose a country, tell me why. Ms. Selecky?

Ms. SELECKY. Well, I will venture a guess. And it is only because of our recent experience with British Columbia. Because we are both a State and a province that have such international trade from the east. And what we look at is the systems are so different. When I sit with my colleagues from Canada and understand that the healthcare system is the governmental system, and that a singular decision is then carried out in a way that is very different with the suasion that we have to do with our private partners, the private suppliers, etc.

It is a very different system. So I am not sure it is better, but, indeed, when they were facing.

Mr. SHAYS. When it comes to dealing with an epidemic, a pandemic, they may be better able to deal with it, given that they have a more public process throughout?

Ms. SELECKY. They are easier to get a common decision through a number of partners, where I, as a State health official, need to work with my public and private hospital systems and convince them. They do it with us.

Mr. SHAYS. It just triggers a reaction from me. We are not going to see that system in the United States, so it is incumbent on all of us to find a way that we make the private and public sector work better. And giving better direction to the private sector, providing financial incentives, dealing with some risk that you encounter, all of that, it seems to me, will play a role in our providing a better service.

So let me end with that, if I could, and thank you all for this hearing. Thank you for being here. Thank you for helping your country do a better job.

With that, we will adjourn this hearing.

[Whereupon, at 12:38 p.m., the committee was adjourned.]

[NOTE.—The Association of State and Territorial Health Officials November 2002 report entitled, "Preparedness Planning for State Health Officials, Nature's Terrorist Attack Pandemic Influenza," may be found in committee files.]

[The prepared statements of Hon. Dan Burton, Hon. Jon C. Porter, and Hon. Diane E. Watson, and additional information submitted for the hearing record follows:]

Opening Statement
Honorable Dan Burton
Committee on Government Reform
Hearing: "The Next Flu Pandemic: Evaluating U.S. Readiness"
Date: Thursday, June 30, 2005

Mr. Chairman, thank you for convening this important and timely hearing to recognize the ever-growing danger of a flu virus striking the United States, and whether or not the United States is adequately prepared to handle a global communicable disease outbreak. I look forward to hearing testimony from our witnesses and hope that by day's end we will have a better idea of how to address this potentially deadly outbreak.

As you know, U.S. health officials have warned us for years that the largest public health threat facing the world today is a flu pandemic. In fact, many officials have estimated that an influenza outbreak could lead to the deaths of more than a half-million people. The United States must continue to do more in order to ensure that we will not be adversely affected by an influenza pandemic. Unfortunately, the United States has experienced – over the recent year – major vaccine shortages. With seasonal influenza deaths of 36,000 and 114,000 hospitalizations, we must work together to address this growing concern.

As we all know, early detection and rapid development of effective vaccines is the best way to defend the public against the influenza virus. One such company who is actively helping to defend the public against a potential pandemic is Roche, Incorporated. As the Member of Congress who has the distinct honor of representing the headquarters of Roche Diagnostics – and its 3,500 employees – in Indianapolis, Indiana, I have had the opportunity to become familiar with the tremendous contributions that Roche and its employees have made to healthcare and diagnostics, and I am impressed with how Roche's investments in research and innovation have yielded inventions to help thousands of people throughout the world. As a result of these investments, people suffering from numerous diseases can now successfully manage their conditions, and doctors and hospitals can more accurately identify illnesses and effectively treat their patients according to the patients' individual needs.

One such investment in innovation is Tamiflu – the first oral medication effective against types A and B of the influenza virus. As I have been informed, Tamiflu is the number one antiviral in the U.S. for treatment and prevention of influenza. Roche has invested significant resources in the development and approval of Tamiflu to bring this product to market as quickly as possible. In fact, Roche has increased manufacturing capacity eightfold in recent years to meet commercial and government pandemic stockpile goals. Moreover, I would like to personally welcome Mr. George Abercrombie – Chief Executive Officer and President – from Hoffmann-La Roche, Inc.

Once again Mr. Chairman, thank you for highlighting the importance of this critical issue. I look forward to hearing the testimony of the Committee's witnesses.

CONGRESSMAN JON C. PORTER (R-NV-3)
COMMITTEE ON GOVERNMENT REFORM
"The Next Flu Pandemic: Evaluating U.S. Readiness"
June 29, 2005

Mr. Chairman, thank you for holding this hearing today. I would also like to thank the witnesses for being here today.

As stated in the Government Reform Committee's background memorandum for this hearing, history indicates that flu pandemics can be expected to occur three to four times each century. Pandemics can be devastating, as seen in the Spanish flu pandemic where 40-50 million died circa 1918, and the next pandemic could occur within the next five years. The scary fact is that, with the advent of aircraft and the vast improvement of various modes of transportation, the next flu pandemic has the potential of being even more devastating if we are not properly prepared.

With the increase in technology we have seen in recent years has come an increase in medical innovation. Flu shots have been able to keep many millions of people from falling ill; however, vaccines alone cannot stop the flu from spreading. Furthermore, last year, Americans witnessed a vaccine shortage where thousands of individuals were unable to get a flu shot. As the flu vaccine shortage showed, our government needs to be prepared on multiple levels with respect to having enough vaccines or anti-virals to sustain the American people should a flu, or other type of pandemic, occur.

Mr. Chairman, I am glad that we are holding this hearing before this year's flu season starts. I believe that last year's vaccine shortage was truly an exercise in our nation's ability to effectively produce and distribute flu vaccines. We should learn from these mistakes and ensure that our country is not left in a vulnerable position when the next flu pandemic hits.

Again, thank you for holding this hearing today, and I look forward to hearing the testimony from the witnesses.

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Opening Statement
Congresswoman Diane E. Watson
Government Reform Committee

Hearing entitled "The Next Flu Pandemic: Evaluating U.S. Readiness"
6/30/05

Thank you Mr. Chairman. The Government Reform Committee has an important public service to perform in regards to the ever-present flu virus. Biological preparedness is considered crucial in the current world climate. Our government has limited control over a natural phenomenon that will threaten citizens every year. Flu pandemic has the ability to cause death in catastrophic proportions.

In its cyclical nature, the annual flu epidemic is a situation that our federal, state, and local health officials try to plan for. Flu pandemic is a worldwide event that is also cyclical. This government would be remiss to not be properly prepared and informed about options to protect the public.

With only two FDA approved vaccine manufacturers (Chiron and Aventis) producing flu

vaccines each year, Congress must consider what can be done to strengthen the market and increase domestic production capabilities. Is a stockpile of antiviral drugs the best way to approach the absent vaccine?

Mr. Chairman, I am concerned about our national position in a very sensitive health care area. In the future, should a flu pandemic occur, it can be theorized that the UK could restrict Chiron's vaccine supply, again resulting in the loss of half of the U.S. flu vaccine supply. Currently, Aventis has the only U.S. based flu vaccine production facility in operation. To address the flu vaccine issue Congress must work to reinvigorate the domestic manufacture of vaccines.

Mr. Chairman, I look forward to today's testimony, and the positive solutions that our witness can provide. I am interested to hear their assessment of the usefulness of antiviral drugs. I am encouraged by the antiviral ability to stem the conditions of the flu. Congress must weigh the feasibility of supplying the suggested antiviral dosage for 25% of the population or decide if the resources should be balanced or directed to another proactive path. We need a much

better system in place to accommodate flu vaccine shortage or increased demand situations. I urge Congress to move forward in the decision making process. I again commend our Committee for a quick response to a serious public concern.

I yield back the balance of my time.

sanofi pasteur
The vaccines business of sanofi-aventis Group

PHILIP HOSBACH

VICE PRESIDENT, IMMUNIZATION POLICY AND GOVERNMENT AFFAIRS

SANOFI PASTEUR

BEFORE THE UNITED STATES HOUSE OF REPRESENTATIVES

COMMITTEE ON GOVERNMENT REFORM

REGARDING

THE NEXT FLU PANDEMIC: EVALUATING U.S. READINESS

WRITTEN TESTIMONY

6/30/05

sanofi pasteur . Discovery Drive . Swiftwater, Pennsylvania 18370 . Tel . : 570 839 7187 . www.sanofipasteur.us
Sanofi Pasteur Inc.

Sanofi pasteur is committed to working with the federal government to develop a safe and effective vaccine to protect the American public in the event of an influenza pandemic. Our common goal is to provide sufficient vaccine for 300 million Americans within the first 12- to 18-month period of a pandemic, and we welcome the chance to provide the committee with our perspective on this important public health issue.

Sanofi pasteur, the world's largest influenza vaccine manufacturer, also produces vaccines against more than 20 different diseases. Worldwide, we produce almost 1 billion doses of vaccines annually. The company, which employs more than 9,000 employees worldwide, is headquartered in Lyon, France. Sanofi pasteur's US operations are located in the Pocono Mountains in Swiftwater, Pa., at a site where vaccine has been produced for more than 100 years. Influenza vaccine has been produced in this facility for more than 30 years and 95% of this vaccine is used exclusively to supply the United States. Sanofi pasteur also has an influenza vaccine production facility in France that supplies other markets.

During the past decade, sanofi pasteur has reliably and consistently increased production of influenza vaccine in the US. Last year, we produced 58 million doses for the US market. We continue to expand our vaccine manufacturing capacity in Pennsylvania and have embarked on the largest infrastructure investment in the company's history, spending almost $80 million to build a new formulation and filling facility. We are also in the final design phases of our influenza vaccine facility expansion, which will significantly increase our US production capabilities.

Pandemic Overview

An influenza pandemic is a global epidemic that has the potential for severe morbidity and mortality.

Three influenza pandemics occurred during the 20th century: the 1918-1919 Spanish flu pandemic, the 1957 Asian flu pandemic and the 1968 Hong Kong flu pandemic. The Spanish flu pandemic was the most severe, causing over 500,000 deaths in the US and an estimated 20 to 40 million deaths worldwide.

The prospect of a pandemic is taking on increasing urgency because of the emergence of an H5N1 avian influenza strain in Southeast Asia 17 months ago. It continues to circulate and has the potential to mutate and become a human pandemic strain. As of June 16th, it has infected at least 103 people and killed more than half of its victims.[1] This is a completely new strain and epidemiologists believe the American population would be at risk if it spreads between humans.

Many experts believe that if this H5N1 virus sparks the next pandemic, it would most closely resemble the 1918 pandemic in terms of morbidity and mortality.[2]

According to the World Health Organization (WHO), the next pandemic is likely to result in 1 to 2.3 million hospitalizations and 280,000 to 650,000 deaths in industrialized nations alone. The US Centers for Disease Control and Prevention (CDC) estimated that as many as 207,000 Americans could die and up to 734,000 could be hospitalized during the next pandemic. Other estimates are even higher. For example, extrapolating from the 1918-1919 Spanish Flu, the US alone could face more than 1 million fatalities. Studies have estimated certain costs of an influenza pandemic in the US as high as $200 billion (FY2005 dollars). These estimates include only direct costs of medical care and indirect costs of lost productivity and

[1] Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO. See WHO site listing under Communicable Disease Surveillance and Response (CSR).

[2] Osterholm MT. Preparing for the next pandemic. *N Engl J Med.* 2005 May 5;352(18):1839-42

mortality rates. Some experts have predicted that a major pandemic could bring the global economy to a halt.[3]

Sanofi pasteur recognizes the urgency of adequate preparation for a pandemic event and is taking steps to be ready.

Progress to Date

We believe the expertise of vaccine manufacturers, particularly those with a track record in influenza vaccine production and distribution, should be utilized early in the planning process. Vaccines, by their very nature, are challenging to develop, produce and distribute. Manufacturers have a unique understanding of these challenges and can provide valuable process and policy input. Our knowledge and experience with the complexities of vaccine supply make industry an essential partner in pandemic planning and policy formulation.

The enormous public health threat posed by a potential pandemic prompted sanofi pasteur to establish an internal working group to examine pandemic planning. We formed a global working group to examine preparedness, production, communications and distribution issues. In the US, we have worked in cooperation with the US Department of Health and Human Services (HHS) to exchange ideas on how best to prepare for and respond to a pandemic influenza outbreak, and have provided significant input into the initial draft of its pandemic plan.

[3] Osterholm MT. Preparing for the next pandemic. *N Engl J Med.* 2005 May 5;352(18):1839-42

We have moved forward with clinical research and vaccine production because of important funding provided by Congress and the Administration. In May 2004, sanofi pasteur entered into the first of four pandemic agreements with the US government. The National Institute of Allergy and Infectious Diseases (NIAID) contracted with us to produce an investigational influenza vaccine based on the currently circulating H5N1 avian influenza virus strain. On March 10, 2005, in accordance with that agreement, sanofi pasteur delivered more than 8,000 investigational doses, which currently are being used in NIH-conducted clinical trials.

In September 2004, the company was awarded a second contract by HHS to produce two million bulk doses of an attenuated version of the same H5N1 avian influenza virus strain of vaccine. This contract represents an important step in gaining experience producing pandemic influenza vaccine on a large scale. This is critical because scale-up presents unique challenges in vaccine production. Part of our agreement is to determine the stability of this vaccine, which is important for understanding our ability to establish an H5N1 reserve.

Sanofi pasteur subsequently entered into a third agreement with HHS to establish and maintain flocks of egg-laying hens and to maintain other essential supplies. The goal is to ensure our ability to manufacture pandemic influenza vaccine at current full capacity levels on a year-round basis. Until now, egg availability has existed only on a seasonal basis to support normal influenza vaccine production. The agreement also calls for sanofi pasteur to manufacture, on an annual basis, investigational influenza vaccine of a candidate pandemic-like strain. Each year, HHS will identify the strain to be used in the investigational lot and will provide the reference virus on which each investigational lot will be based. This will enable us to gain experience working with various viral strains that might be similar to the next pandemic strain.

Finally, in April 2005, sanofi pasteur was awarded a fourth contract from HHS. This was to speed the development process for a new cell culture influenza vaccine in the US and to deliver plans to establish a US-based cell culture influenza vaccine manufacturing facility.

Required Action:

We are encouraged by the increased attention pandemic planning is receiving from the US government, industry, international agencies and key stakeholders. However, unresolved critical issues remain. The failure to address these challenges could adversely affect our country's ability to respond to a pandemic event.

I would like to briefly outline steps that should be taken to help the country better prepare for a pandemic and minimize the effects should one occur.

A first step is to steadily increase interpandemic influenza immunization rates. Manufacturers will respond to increased and predictable demand by producing additional vaccine to fulfill this demand.

This is important because our ability to produce and administer large quantities of influenza vaccine during interpandemic periods will enable a more rapid response during a pandemic. Increasing capacity in dedicated influenza vaccine production facilities and establishing an infrastructure that can deliver vaccine and immunize large numbers of people in a short period of time is a key component of pandemic preparedness.

To that end, Congress, industry and stakeholders need to work together to encourage higher influenza immunization rates in accordance with HHS' Healthy People 2010 immunization goals. The objective is to

immunize approximately 180 million Americans. However, as a nation, we have never immunized more than 85 million people in any given year. This is unacceptable. A steady and sustained increase in interpandemic demand would give current manufacturers the confidence to continue expansion plans and new companies the incentive to enter the market.

Second, we need to ensure a proper combination of private and public sector distribution of vaccine in the event of a pandemic. We believe that while it will be important to establish mechanisms for mass immunizations and clinics, the private physicians' offices will continue to play a vital role as well. During a typical influenza season, the private sector distributes more than 85% of the nation's influenza vaccine supply. The private market provides maximum flexibility in vaccine distribution and allows us to reach large segments of the US population in their "medical homes." This includes the elderly, who should not stand in long lines and may be more comfortable with their personal physicians.

Last year's influenza vaccine shortage illustrated sanofi pasteur's unique expertise in processing and shipping product to virtually any location in the United States within 24-48 hours. We shipped vaccines to end-users in accordance with the CDC's recommendations and distribution plan. Further, the unprecedented degree of collaboration between sanofi pasteur and the CDC underscores our willingness to work with public agencies to protect America's public health. This year, sanofi pasteur has modified our ordering process to provide that, in the event of another shortage, available vaccine reaches high-risk people first. All of our "pre-book" customers are being asked to estimate what percentage of the vaccine they are requesting will be used for priority patients. The systems utilized to collect these data and the ability to easily identify priority recipients, as specified by federal, state and local governments, will be key in protecting the public health in the event of a pandemic. We also believe that there should be greater funding for coordinating

communications between federal and state agencies and the private sector regarding vaccine allocation issues.

Pandemic influenza vaccine liability protection is another critical issue in pandemic preparedness. A special compensation and liability protection program will need to be established similar to the 1976 swine flu and 2002 smallpox model. Liability protection for companies is essential to ensure that manufacturers are able to fully participate in the development and licensure of a pandemic vaccine. This is of paramount importance. The new program should be completely distinct and separate from the existing Vaccine Injury Compensation Program (VICP). It should focus exclusively on liability protection for a monovalent influenza pandemic vaccine, precisely the type of vaccine that will be produced in a pandemic event. The failure to offer liability protection on a timely basis could have profound implications for the actual testing and development of large-scale production of vaccine, leaving the nation unprepared. It is important to address liability issues before a health emergency arises. This ensures that pandemic vaccines will be developed, economic costs will be mitigated, and the potential for needless and costly litigation will be curtailed.

We strongly urge Congress to consider -- and establish -- liability protections that are as strong as those afforded providers of smallpox vaccine under the Homeland Security Act of 2002. Vaccine liability provisions ensure that we can bring a pandemic influenza vaccine to market as quickly as possible.

Sanofi pasteur is committed to protecting America's public health in the fight against influenza through vaccinations. We want to commend Congress and the Administration for dedicating time and resources to this critical area. Thank you for giving us the opportunity to express our views on this important issue.