TESTIMONY OF

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TO THE

CHAIR OF THE ASSEMBLY BUDGET COMMITTEE
ON HEALTH AND HUMAN SERVICES
CALIFORNIA ASSEMBLY

CALIFORNIA'S LEVEL OF PREPAREDNESS FOR AN OUTBREAK OF AVIAN INFLUENZA

NOVEMBER 4, 2005

Mr. Chairman, distinguished Members, it is an honor to appear before you to present viewpoints on California's level of preparedness for an avian influenza outbreak. My perspective is derived from experience as an Associate Professor of Epidemiology at the UCLA School of Public Health, as a physician trained in internal medicine and infectious diseases, and as a scientist working to implement a high-throughput laboratory surveillance network against influenza and other threatening infectious diseases. Real-time surveillance capabilities, in California and worldwide, are a cornerstone for responding effectively to the public health challenges of pandemic influenza.

By way of introduction, I received the B.A. degree (Chemistry) in 1976 from DePauw University, the M.D. degree in 1980 from Case Western Reserve University, and graduate education in applied physics at Stanford University. I am Board Certified in Internal Medicine (1997) and Infectious Diseases (1998), with a fellowship in adult infectious diseases from UCLA. From 1982 to 1986 I served as Postdoctoral Fellow and Staff Member at the Los Alamos National Laboratory and from 1986 to 1992 as a Physicist at the Lawrence Livermore National Laboratory. After medicine residency at the UCLA School of Medicine from 1992 to 1994, I joined the UCLA School of Public Health as an Associate Professor of Epidemiology.

My cross disciplinary work involves biology, physics, and policy related issues. I have authored over 45 publications (some of these on influenza), including three U.S. patents on methods to access and operate high-throughput laboratories. I am an editor of *Firepower in the Lab: Automation in the Fight Against Infectious Diseases and Bioterrorism* published by Joseph Henry Press in 2001 and also of *Jane's Chem-Bio Handbook, second edition.* In 1988, I organized the workshop *A National Effort to Model AIDS Epidemiology* for the Office of Science and Technology Policy (OSTP) and oversaw the publication of a White House report that helped to influence AIDS research priorities in the United States. In 1999, I also organized the meeting *Automation in Threat Reduction and Infectious Disease Research: Needs and New Direction* under the auspices of the Institute of Medicine and National Academy of Engineering. At present, I teach graduate level courses at UCLA on infectious diseases (including pandemic influenza), mathematical modeling and analysis of infectious diseases, and public health responses to bioterrorism. I also serve as a guest scientist at the Los Alamos National Laboratory in New Mexico, and as an instructor on bioterrorism preparation and response for the U.S. Department of Homeland Security and lectures throughout America in this capacity.

Epidemic versus Pandemic Influenza

The "life" of a virus involves *reproduction*, *mutation*, and *selection*. Along these lines, influenza is a relentless and ever changing disease. It infects humans, farm animals, wild migratory birds, and a host of other animals. In humans, influenza is transmitted from person to person by droplet aerosols or by exposure to contaminated surfaces. In certain animals, especially birds, influenza is transmitted by fecal-oral routes.

In humans, influenza cases increase and peak in the winter months (October to March in the northern hemisphere) and subside in the summer months. Every year, so-called "epidemic" strains of influenza infect 600 to 1,200 million people worldwide and are attributed to 500,000 to 1,000,000 deaths worldwide, with 25,000 to 45,000 deaths in the United States. In addition, epidemic influenza accounts for numerous hospitalizations, secondary bacterial pneumonias, middle ear infections in infants and children yearly. Literally tons of antibiotics are consumed to treat these complications worldwide. Economic impacts include lost work and productivity in our labor force.

Twice a year, the World Health Organization (WHO) organizes a formal meeting with its collaborating center directors to review information on circulating influenza strains. This advisory committee identifies circulating strains that new vaccine formulations should target. Consequently, approximately 280 million doses of trivalent influenza vaccine are manufactured worldwide each year to reduce the severity of influenza infection, with 80 to 90 million doses administered in the United States. Once the WHO offers its recommendations for vaccine strains, it takes roughly six months to scale up, manufacture, and deliver egg-based influenza vaccines to health care providers.

Influenza pandemics occur when the virus takes on an entirely new form that is "novel" or previously unseen by the human population. In the 20th century, there have been three influenza pandemics. The 1918 pandemic killed at least 40 million people worldwide when the global problem was just 1.75 billion and, for unknown reasons, exhibited greater lethality for people 25 to 45 years old. The 1957 and 1968 pandemics were milder and killed 1 to 4 million people worldwide — mostly the very young, the very old, and also those with weakening illnesses.

Now we are preparing for the first influenza pandemic of the 21st century. The origins of so-called *highly pathological avian flu*, or H5N1 bird flu, go back several years. In 1997, an outbreak of avian H5N1 influenza swept through poultry flocks in Hong Kong, killing nearly 100% of chickens farm by farm. In May 1997, it killed an otherwise healthy three year old boy and it took nearly four months to discover that he died from a novel or "shifted" strain of influenza. From November to December 1997, 17 more people became infected with avian H5N1 influenza avian — 5 of these 17 people died. Confronted with a case fatality of 33% (6 out of 18 people), health authorities opted to destroy all 1.5 million chickens in Hong Kong and the entire affair transpired so quickly that very little scientific, or laboratory based, information was available to guide health authorities as they struggled with truly monumental decisions.

In 2004, a related but mutated strain of highly pathologic avian influenza reemerged in southeast Asia. To date, it has resulted in over 140 known human cases and about 70 deaths, which translates to a case fatality of 50%. In 2004 and the first half of 2005, the involved countries included Vietnam, Thailand, Cambodia, and Indonesia. In an attempt to control this outbreak of avian H5N1, over 150 million birds have been destroyed, resulting in the equivalent of billions of dollars in economic losses. In the second half of 2005, avian H5N1 influenza appears to have been carried by wild migratory birds to northern China, Mongolia, Tibet, Kazakhstan, and siberian Russia. It has further spread to Turkey, Romania, Bulgaria, Greece, Macedonia, and Croatia. At the time of this hearing, avian H5N1 influenza may be spreading to Africa and North America. A year ago, people spoke of "containing" or "eradicating" avian H5N1 influenza. But this virus has now established itself in too many places to entertain this notion.

My education and formal training are in human public health and human infectious diseases, not in the veterinary disciplines. Nevertheless, I can offer a very well informed appraisal of the overall threat that California faces with respect to avian H5N1 influenza. There is every reason to believe that avian H5N1 influenza will spread worldwide. It will likely be introduced to north America via wild bird flyways that link Asia and Russia to Alaska and, through another circuit of flyways, link Canada, the United States, and California to Alaska. Once avian H5N1 influenza reaches Alaska, veterinary and migratory bird specialists suggest that it will be "only a matter of weeks — not months" for avian H5N1 to reach our State of California.

We therefore face two threats. The first is spread of highly pathologic avian influenza to California and its establishment in wild birds and domestic poultry. The odds of this happening are rather high — likely greater than 90%. The second is that one or more mutations of avian H5N1 influenza will spontaneously arise (somewhere in the world through the ongoing processes of viral reproduction, mutation, and selection) that enables avian H5N1 to spread efficiently from human to human. The odds of this happening are unknown and there is insufficient scientific information on influenza viruses on which to base reliable estimates. But even if the odds are relatively low — say less than 10% — they are not grounds for complacency.

Impact on California

If avian H5N1 influenza remains an agricultural pathogen and only incidentally infects humans, who have had close contact with infected birds, it will still have a major impact on the State of California. Our State ranks #9 among poultry producers in the United States. Overall, the California poultry industry has sales in excess of $2.5 billion annually and provides jobs to 25,000 people statewide and, indirectly, to thousands more in associated industries including trucking and feed supplies. In the agricultural outbreak scenario, occupational health and safety issues associated with incidental avian H5N1 influenza infections and reluctance of the public to purchase and consume poultry cannot be underestimated. In Europe, where avian H5N1 influenza is spreading, poultry sales and poultry consumption have fallen by over 25% in the past month. In addition, some California's have birds flocks in their back yards that could become infected and pose yet another source for incidental human infections. Like Asia, the total number of incidental human infections could reach into the hundreds yearly. Workers' liability and physiological impacts of these incidental human cases would take on a life of their own.

The formal definition of an influenza pandemic includes infection of over 25% of the population. In California, there are about 35 million people. So infections in 25% of the population sum to roughly 9 million people. If we assume a case fatality of 2%, or about that of the 1918 pandemic, the estimates translate into 180,000 influenza associated deaths in California alone. In addition, there would be an overwhelming number of people, perhaps as many as one million, requiring hospitalization and/or urgent medical care. As noted by Dr. Linda Rosenstock, Dean of the UCLA School of Public Health, in yesterday's Los Angeles Times the costs will be "heaped onto health systems already under pressure to meet daily needs." I concur with this assessment. Surge capacity in the current health care delivery system is very limited and funding to prepare is also very limited.

Pandemic Influenza Plan

The Pandemic Influenza Preparedness plan released by the U.S. Department of Health and Human Services on November 2, 2005 emphasizes three pillars: I) Preparedness and Communication; II) Surveillance and Detection; and III) Response and Containment. A summary of each is as follows.

Pillar one encompasses planning for a pandemic, communicating expectations and responsibilities, producing and stockpiling vaccines, antivirals and medical materials, establishing distribution plans for vaccines and antivirals, and advancing scientific knowledge and accelerating development.

Pillar two encompasses ensuring rapid reporting of outbreaks, and using surveillance to limit speed.

Pillar three encompasses containing outbreaks, leveraging national medical and public health surge capacity, sustaining infrastructure, essential services and the economy, and ensuring effective risk communication.

The Pandemic Influenza Preparedness plan also outlines roles and responsibilities at multiple levels including the federal government, states and localities, private sector and critical infrastructure entities, individuals and families, and international partners.

In September 2001, the California Department of Health Services also released its Influenza Pandemic Response Plan. In light of the new federal Pandemic Influenza Preparedness plan, just released by the U.S. Department of Health and Human Services on November 2, 2005, it would seem appropriate for California to reexamine and evaluate whether to update their overall plan.

The outbreak of avian H5N1 influenza in Hong Kong in 1997 and the fast paced decision to destroy food producing poultry demonstrates that health officials will be called upon to make monumental decisions — regardless of whether avian H5N1 remains an agricultural pathogen only or whether avian H5N1 evolves into an efficient (airborne) human to human pathogen. In order to make such decisions, officials and authorities will need rapid, accurate, and up-to-date information on the geographic location of avian H5N1 influenza and on the genetic mutations taking place in the virus.

For the remainder of my testimony, I would like to focus on pillar two of the Pandemic Influenza Preparedness plan. This pillar pertains to infectious disease surveillance, analysis, and response efforts and to the urgent need for real-time laboratory based information to sustain such efforts.

Influenza Surveillance: The Demand to Expand

The Global Influenza Surveillance network, coordinated under the auspices of the WHO, is the most extensive infectious disease surveillance system in existence. It involves 85 countries at 110 institutions worldwide. In the 2003 to 2004 season, 157,759 samples were collected from people exhibiting influenza like illnesses. Of these 23,549 samples (15%) tested influenza positive, the rest tested influenza negative. 17,768 samples contained influenza A and 5,799 contained influenza B, with 18 subtyped as A/H1N1 and 5,801 as A/H3N2. In the final analysis, however, fever than 1,000 influenza samples underwent comprehensive laboratory analysis (immunotyping, whole genome sequencing, and antiviral susceptibility/resistance testing) at one of four WHO Collaborating Centers, located in the United States, United Kingdom, Japan, and Australia. Since there were one billion cases of influenza worldwide that season, fewer than one sample per one million cases underwent such detailed laboratory analysis. Moreover, the time delays to complete such detailed analysis ranged from weeks to months. In light of avian H5N1's relentless geographic spread, such delays can be costly and disastrous.

In the same 2003 to 2004 season, a total of 167 samples were subtyped as A/H1N1 or A/H3N2 from the State of California. A small fraction were forwarded to the Centers for Disease Control and Prevention in Atlanta, GA for more detailed laboratory testing. Since there were at least 3.5 million cases of influenza in California that season, fewer than one sample per one million cases also underwent more detailed laboratory analysis. Like the rest of the world, California's ability to type, subtype, and test influenza in greater detail is dangerously limited.

High-Throughput Laboratory Network

On September 7, 2001, I authored a lead editorial in the journal Science titled *A Global Lab Against Influenza* that called for creating a new kind of high-throughput (high speed, high volume) laboratory network against threatening infectious diseases. The plan makes use of existing capabilities and infrastructures: sample collection, airfreight, Internet, testing procedures, high-throughput equipment, and fast computers. Four years later, the plans outlined in this editorial are more pressing than ever.

The high-throughput laboratory network is absolutely essential to enable the United States and the State of California to cope effectively with the likely spread of avian influenza, as well as other deadly infectious diseases. The lab will provide the rapid, accurate, and up-to-date information needed to deal with an outbreak that is not available today.

Surveillance teams will be able to go to the source of the outbreak, record epidemiologic observations, and collect samples that can be quickly sent to the laboratory. The questionnaire would run on inexpensive pocket devices (for example, Palm handhelds or even cell phones). Bar codes will be used to link samples to their corresponding questionnaires. Completed questionnaires will be e-mailed to the high-throughput laboratory network, where they will form the basis for seeking associations between population and laboratory data.

The laboratory's high-throughput automation equipment will process and sequence the influenza genes in these samples 24 hours per day, seven days per week. All the influenza genes will be accurately sequenced and associated with field observations. Such up-to-date field surveillance and laboratory firepower have not been combined at present. The practical applications of the high-throughput laboratory network to an avian flu epidemic or pandemic are several, as summarized below.

1. Emergency Outbreak Control with Tamifu. Scientists have proposed using the drug Tamiflu to halt an avian influenza outbreak in humans. The strategy is to administer millions of Tamiflu doses (ring prophylaxis and/or treatment) to the stricken population and surrounding geographic zone within weeks. Immediate recognition of the outbreak and rapid surveillance to determine its size are therefore critical. At some point, Tamiflu resistant avian influenza viruses will likely emerge, representing a threat to emergency control efforts, and health authorities will need real-time information on their location and number. Such emergency interventions will generate hundreds to thousands of samples for laboratory analysis within days. Given current laboratory surge capacity, the proposed high-throughput laboratory will be the only feasible means to meet the challenge.

2. Pandemic Vaccine Strain Selection. Twice yearly, as mentioned above, the WHO organizes formal meetings to identify circulating influenza strains that new vaccine formulations should target. After a review by national health authorities, vaccine manufacturers have roughly 6 months for scale-up, production in eggs, and distribution. Health care services then have another 3 months to administer 280 million doses of trivalent vaccine worldwide. The 1918 influenza swept the world within 6 to 12 months. In the event of a new avian influenza pandemic, the United States will rush to manufacture and deliver new targeted vaccines. On August 7, 2005 the media reported that a promising avian influenza vaccine prototype had been tested. Even if this vaccine should prove to be fully effective, the virus can mutate and render it ineffective. This is precisely what happened with the vaccine developed after the 1997 avian influenza outbreak in Hong Kong. The strain targeted by that vaccine has since maturated and this could easily happen again. That is why the up-to-date information provided by the high-throughput laboratory remains more essential than ever.

The high-throughput laboratory will help to protect lives in two ways. It will provide faster information for vaccine strain selection, potentially saving one to two months in vaccine delivery. It will also continuously monitor for the emergence of escaping influenza strains and thereby guide critical decisions to update pandemic vaccines or use them in combination with limited supplies of antiviral drugs. Drug companies are developing modern molecular methods to manufacture influenza vaccines that could cut delivery times in half. Within the next few years, these new molecular based methods in combination with the proposed high-throughput laboratory will help to reduce vaccine delivery time and in so doing save lives.

3. Enhancing Human Surveillance. Despite its sophistication, the WHO Influenza Program has limitations. First, current laboratory methods for characterizing influenza are time consuming and labor-intensive. As mentioned above, only a small number, fewer than 1,000 samples, undergo definitive characterization by the CDC and the three overseas collaborating centers. Second, it could take weeks or months to detect and analyze an unusual or unexpected influenza strain and to understand its significance. Delays can be costly or disastrous.

The high-throughput laboratory would be capable of analyzing influenza genes from10,000 samples per year. It would create a capacity that is far faster and at least 10-fold greater than currently exists to fully characterize the influenza virus as it evolves.

4. Enhancing Animal Surveillance. Highly pathologic avian influenza is known to infect different migratory birds. When the virus is carried by birds from location to location, it will likely jump from species to species. Efforts to spot the spread of avian influenza from Asia and Russia to North America must therefore be geared to match wild bird sampling in the field with adequate laboratory capacity. At present, the University of California is expanding statewide efforts to capture wild birds, identify them, and preserve swab samples for influenza virus detection. This important effort will lead to new information on which birds carry influenza viruses and, since birds migrate from Alaska to the continental United States routinely, will serve as an avian influenza warning system.

If an avian influenza outbreak occurs in North America, the number of samples collected will soar. The USDA operates an animal health laboratory network but it can be easily flooded by fast paced and large scale outbreaks. It is also geared to detect (positive/negative) influenza viruses, not to perform detailed analysis for monitoring viral evolution and bird carrier patterns.

In summary, a new kind of high-throughput laboratory network will strengthen our public health infrastructure against avian influenza and other threatening infectious diseases — it's dual use. With adequate funding, the high-throughput laboratory network could be up and running within 12 to 18 months.

Again, I appreciate the opportunity to present this information. I shall be happy to answer your questions and to provide additional documentation supporting the material presented.

AGENDA

ASSEMBLY BUDGET SUBCOMMITTEE NO. 1
ON HEALTH AND HUMAN SERVICES
AND
ASSEMBLY HEALTH COMMITTEE

Assemblymember Hector De La Torre and Chan, Co-Chairs

NOVEMBER 4, 2005, 11:30 AM

UCLA JAMES WEST ALUMNI CENTER
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Avian Flu: Is California Prepared?

1. **Avian Flu: What is it and Why the Concern?**
   - **Scott P. Layne, MD, Associate Professor, Department of Epidemiology, UCLA School of Public Health**
2. **Status of the State's Plans for an Outbreak**
   - **Sandra Shewry, Director, Department of Health Services**
   - **Kevin Reilly, DVM, M.P.V.M., Deputy Director, Prevention Services, Department of Health services**
3. **Overview of State Audit on California's Preparedness for Infectious Disease Emergencies**
   - **Steve Hendrickson, Chief Deputy State Auditor, Bureau of State Audits**
4. **Status of the Front Lines**
   - **Jonathan Fielding, MD, Los Angeles County Health Officer**

5. **Impact of Pandemic on the Availability of Hospital Beds**
   Hospital Representatives

   - **Martin Gallegos, D.C., Senior Vice President/Chief Legislative Advocate, California Hospital Association, Sacramento**
   - **Ramon Perez, M.D., Infectious Disease Consultant, Anaheim Memorial Medical Center, Anaheim**

6. **The Role of the Biomedical Industry**

   - **Barbara Morrow, Vice President-General Counsel, California Healthcare Institute (CHI)**

7. **Public Comment**