

Strategies for Prevention and Response to Public Health Crises

Emerging infections, including pandemic infectious disease presents a major public health threat to the United States and the world, yet the nature of the threat and the measures necessary to mitigate it are poorly understood. While the prospects of avian flu are unknown, the annual morbidity caused by routine infectious diseases such as seasonal influenza suggests the scope of the problem. According to the American Society for Microbiology¹, influenza and pneumonia are the leading infectious causes of death in the United States and rank seventh among all causes of death worldwide. Influenza viruses regularly mutate resulting in new strains periodically that move from animal hosts to humans. On average, influenza accounts for 36,000 deaths and 200,000 hospitalizations in the United States each year. Far more deadly, though, were three influenza pandemics – Spanish influenza in 1918, Asian influenza in 1957, and Hong Kong influenza in 1968.

While no one can predict the timing or source of the next pandemic, epidemiologists agree that a future pandemic is inevitable, and is likely to have devastating consequences on global health and economies. Preparedness is thus essential, and will require government and industry collaboration in several areas: expanded research and development of vaccines and improved vaccine manufacturing technology; antiviral medicines; diagnostics; delivery technologies; expanded capacity for stockpiling; education of the public; and plans for surveillance and containment.

¹ "American Society for Microbiology Statement on Pandemic Influenza Plan," written by Michael Leavitt, Secretary of HHS on December 5, 2005. <http://www.asm.org/Policy/index.asp?bid=39508>.

California's life sciences industry, with its extensive academic research, leading biopharmaceutical, medical device and diagnostics companies, and investment in bioinformatics, is committed to working with government and public health agencies, at the state, federal and international level, to develop technologies that can prevent, diagnose and treat infectious diseases, along with other potential threats to society like anthrax.

CHI – California Healthcare Institute, in November 2005, convened an extraordinary group of state and federal healthcare policy makers, medical researchers, and leaders of some of California's most innovative biomedical companies at Gilead Sciences' headquarters in Foster City, Calif., to discuss strategies for prevention and response to the spread of HIV/AIDS, potential biological terror attacks, and the potential for a pandemic of influenza. The rich dialogue broadly addressed three areas:

1. How to mobilize all aspects of society for an influenza pandemic;
2. Lessons learned from combating HIV/AIDS;
3. How the U.S. Food and Drug Administration is pursuing twin goals of increasing safety and expediting new product reviews.

The forum focused on a set of key questions, principles and recommendations that CHI could incorporate into its policy agenda. These include strengthening all aspects of influenza vaccine development, from new methods of production that do not rely on eggs (cell culture)

to production, clinical testing and release; accelerating the production and distribution of antiviral drugs; increasing investment in screening and diagnostic technologies; and procuring and stockpiling needles and syringes together with vaccines.

Ultimately, the information, recommendations, and viewpoints that emerged from the forum will serve to ensure that the biomedical industry and government leaders can more effectively prepare for and respond to a potential national and global public health crisis.

PANDEMIC PERSPECTIVE: THE BIG PICTURE

Richard Preston, Ph.D., best-selling author of books about infectious disease and bioterrorism – *The Hot Zone*, *The Cobra Event*, and *The Demon in the Freezer* – started the forum by describing his investigations in Africa on the origins of the deadly Ebola virus. Progressing to a discussion of anthrax, and how its aerosolization could be turned into a biological weapon, Preston dispersed a small puff of baby powder to powerfully illustrate that the air circulation system could dispense the fine dust quickly throughout the entire room. It was a sobering demonstration, illustrating the ease of dissemination of a potential biologic weapon.

Recalling the 2001 anthrax terror attacks, and reminding forum attendees that the perpetrator of those attacks has never been identified, Preston cautioned that biotechnology has been and likely will again

be used for evil purposes, even as it continues to target important medical needs.

Preston also described our ever present, turbulent and invisible viral “weather” – particularly the propensity of viruses to jump from one endemic host to a new host as a strategy for a virus’ long-term survival. Avian flu, he warned, is already an epizootic (the animal equivalent of a pandemic in humans) for birds, spread through natural migrations of birds as well as, potentially, by humans who smuggle birds around the world. Control presents a paradox: animal vaccine may render birds better carriers and limit antibody testing as a tool to track the spread of virus. He stressed that society is not prepared to respond to either a pandemic caused by a virus that jumps from animal species to humans or biological terrorism. Surveillance of ‘viral weather’ is key, he said, and with any infectious disease, an effective vaccine is the most powerful and effective countermeasure.

Yet in the face of the H5N1 infection, which has killed millions of chickens and other fowl, but whose genetic power to do the same to humans is less clear, developing an efficacious vaccine has proved extremely difficult. Through March 2006, the 186 human infections (and 105 deaths) from avian flu appear to have resulted from direct contact of humans with birds. (Data published in March 2006 found that receptors for avian viruses like H5N1 on human cells are in highest concentration deep

in the lung, and sparse in the upper respiratory tract. This finding is consistent with the high frequency of severe pneumonia in most human H5N1 infections.) Still, most scientists agree that a flu pandemic will occur when one of the 16 types of flu virus in the animal world, probably one that infects birds, manages to switch hosts and spread efficiently between humans. However, they disagree about whether H5 is the likeliest candidate to make such a switch. Earlier pandemics have been caused only by H1- (the 1918 pandemic), H2- (the 1957 Asian flu) or H3-type viruses (the Hong Kong flu of 1968).

When human-to-human transmission occurs, considering the velocity and volume of global air traffic, Preston wondered if governments, communities and businesses could respond in a timely and meaningful fashion. Will we have the antiviral drugs we need? Will we have surge capacity in hospitals and clinics? Preparation at the local level, he cautioned, is critical. Ultimately, despite his sobering questions and warnings, Preston offered a statement of faith in American resiliency, ingenuity, and innovation.

OUTBREAK: MOBILIZING FOR SIGNIFICANT EPIDEMIC

Howard Backer, M.D., *Chief Medical Consultant, Emergency Preparedness, California Department of Health Services* (CDHS) outlined the state’s “Pandemic Preparedness and Response Plan” (www.dhs.ca.gov). He emphasized that pandemic influenza has the potential to

severely disrupt every sector of society and to cause more death than any other public health threat.

Backer emphasized the importance of communication, because no amount of vaccine or antiviral drugs will prepare us sufficiently without transparency: clear, accurate, responsible and timely communication, and that there is a role for both government and the private sector in communicating. Who will, and who will not be treated with scarce but valuable vaccines or antivirals? Who will define those individuals at highest risk of infection and make antiviral medications available? Who will decide whether keeping the death toll as low as possible is as important or more important than maintaining the economy? Because it can take months or years to develop, produce and distribute new vaccines, vaccination to prevent infection at the time of a rapidly spreading pandemic is not a realistic plan. However, there is an immediate critical need to develop influenza vaccines that are more effective and provide longer duration of immunity, especially in more vulnerable geriatric and pediatric populations. While everyone is responsible for preparedness, Backer focused on measures that would enhance the ability of CDHS and local health departments to respond to a pandemic outbreak or other public health emergency:

- Expanding capacity to investigate disease outbreaks
- Increasing communicable disease surveillance and response

- Increasing California’s antiviral drug supply and capacity to manage antiviral drugs and vaccines
- Supporting local health department public health infrastructure
- Mounting an aggressive public health education campaign
- Developing a program for preventing and controlling infections in health care facilities
- Strengthening the state’s laboratory infrastructure and surge capacity

In his 2006-07 budget, Governor Schwarzenegger proposed \$48.5 million to support these improvements in California’s public health preparedness.

Richard Whitley, M.D., *Professor of Pediatrics, Microbiology and Medicine, University of Alabama at Birmingham School of Medicine*, reviewed the background of the avian influenza epizootic, noting that while the original reservoir for the virus is unknown “it turns out that birds are the natural reservoir in general for influenza.” Of the 16 viral subtypes found in birds, however, only six occur in humans. The H5N1 strain circulates widely in birds, but it has never circulated in humans, which means that there is no current population immunity for this subtype. While the H5N1 strain is dangerous, it is not routinely spread by human-to-human contact. Nevertheless, the World Health Organization (WHO) has placed it on alert status because of the potential for mutation.

“Business leaders should give pandemic preparedness at least as much attention as they gave information management around the anticipated Y2K crisis. What happens if 30 percent to 50 percent of your employees can’t come to work?”

– Richard Whitley, M.D.

Whitley’s advice on preparing for a human pandemic includes:

- Vaccine development and production (noting that over the past five years, the U.S. has experienced shortfalls in seasonal influenza vaccine production)
- Development of clear priorities at the federal and state levels to determine who receives vaccines and antiviral drugs in short supply
- Implementing “respiratory hygiene” and isolation measures to interrupt person-to-person transmission of virus

In addition, as it related to biodefense, Whitley talked about the need to develop an improved smallpox vaccine, as well as drugs to treat smallpox. He also noted the problem of endemic polio in the developing world and outlined possible strategies for eradicating the poliovirus. Finally he mentioned the complexity of today’s system of individual institutional review boards (IRBs), explaining that expedited development of experimental drugs would benefit from a centralized, streamlined IRB process.

Frederick Hayden, M.D., *Professor of Internal Medicine and Pathology, University*

of Virginia Health System, in addressing avian flu, highlighted the need for:

- Better veterinary vaccines
- Point-of-care diagnostic assays for avian viruses
- Antiviral drugs: production, stockpiling and research
- Better understanding of how to use existing antiviral medication

Antiviral drugs could make a life or death difference and lessen the death toll in an influenza pandemic. Neuraminidase inhibitors, a class of antivirals commonly known as Tamiflu® from Roche and Relenza® from GlaxoSmithKline, can be used to treat people already infected with influenza. While they do not eliminate the virus, they do reduce its release from infected cells by blocking a key viral enzyme, and they also limit the severity of symptoms – patients who cough less will spread the virus less effectively. The drugs are also effective for prevention and when available in sufficient quantities can be used to protect vulnerable groups. One strategy based on mathematical modeling studies is the use of mass geographically targeted chemoprophylaxis to try to extinguish or delay emergence of an evolving pandemic. Roche and GlaxoSmithKline are working with the WHO and governments around the world to establish rapid response stockpiling.

Hayden advocates additional clinical studies to define the proper dosage for critically ill patients. Because of the potential of influenza

viruses to become resistant to existing drugs, Hayden recommends developing alternative therapies and routes of administration for the currently marketed medicines. In addition, noting that recognition of new viruses, such as avian flu, is a challenge – it requires sophisticated testing of RNA that can only currently be accomplished in a limited number of laboratories – Hayden says point-of-care diagnostic tools that can quickly be used to guide decisions regarding antiviral treatment are critical.

Lance Gordon, Ph.D., *President and CEO, VaxGen*, explained that his company’s bio-defense success following the 2001 anthrax attacks depended on close partnership between industry and government. VaxGen responded to a government Request for Proposal to develop a new anthrax vaccine that came out months after the attacks and was awarded with its first government contract in under a year from the anthrax mailings. One year later, VaxGen produced clinical data supporting the potential of its anthrax vaccine candidate and was awarded a second contract in 2003 to support advanced development and manufacturing scale-up. In 2004 VaxGen was awarded a third contract to supply 75 million doses of a modern anthrax vaccine for civilian defense. The contract, the first of its kind under the Project BioShield Act of 2004, is intended to provide enough product to vaccinate 25 million Americans in a multiple-dose regimen against inhalation anthrax. Based on

To a thoughtful and provocative question from the audience: ***What is the one thing we should be doing now, so we will be ready on the day a pandemic spreads across the world?***

The panelists replied:

- **Vaccinate** widely against seasonal influenza
- **Achieve** the immunization rates (60% of the U.S. population) that are currently recommended
- **Educate** the public regarding simple measures to contain influenza (e.g., cover your cough, telecommute, be prepared to stay at home, etc.)
- **Plan**, produce and stockpile vaccines, antiviral drugs and medical devices
- **Honor** the first responders
- **Instill** a sense of mission in them, and appreciation for their mission
- **Create** a panel of industry and government leaders that will define plans and progress

his extensive knowledge of vaccine development, Gordon observed that because today’s flu vaccines may not be more than 30 to 40 percent effective in high-risk populations, there is an urgent need for better flu vaccines.

J. Leighton Read, M.D., *General Partner, Alloy Ventures*, said government must move faster in its BioShield initiatives. Public health preparedness campaigns to discourage going to work or school with upper respiratory virus

will be important. He also advocated that people become familiar with their local community health departments and first responders, such as fire and police departments and paramedics. “Disasters have the capability to divide people or to bring them together,” he said. “How many of us know the firefighters and paramedics in our communities? We should know them and thank them now, because our appreciation of them and cooperation with them will come back to us in a pandemic situation.”

As for vaccines, Read pointed out the attention and investment going into cell-based technologies to produce vaccines. Use of cell cultures for producing vaccines is promising compared to well-established technology using eggs to produce vaccine because such systems could be rapidly expanded and scaled up in times of emergency. None of the technologies available in the near-term, including cell culture, is likely to provide sufficiently rapid turn-around from identification of a novel strain to bulk production. Right now, our best vaccine strategy is to use our best current guess about strain evolution to create a rolling stockpile of vaccine doses based on current alternatives, including inactivated vaccines, such as the flu shot (with or without adjuvants), and live attenuated vaccines, such as the intranasal vaccine.

Noel Harvey, Ph.D., *Director of Research and External Relations, BD Technologies,*

described the need for the front-line tools that will be needed to fight infectious outbreaks. If thousands of people were infected, the medical device supply chain could break under pressure. Needs include:

- Immediate planning, production and procurement of dose-sparing, safety-engineered syringes to maximize vaccine supplies, as well as masks, ventilators, and hospital beds that are currently in short supply and may be required in a pandemic
- Disposable diagnostic devices that distinguish avian flu from the common cold or other viruses

As for stockpiling supplies, Harvey said “Governments around the world are approaching the medical device industry requesting hundreds of millions of syringe units even without a vaccine currently on hand. We are eager to plan with federal, state, and local government for production and procurement of appropriate syringes so that the needs of our citizens can be served as well.”

John Bishop, CEO, Cepheid, discussed Cepheid’s biohazard detection system now deployed in primary U.S. Postal Service processing centers. Cepheid produces automated fully-integrated systems that perform genetic analysis, including DNA and RNA analysis, for the clinical molecular diagnostic, biothreat, and industrial markets. In order to reduce the dangers posed by biological terrorism and

pandemic diseases, it is necessary to rapidly and accurately detect biothreat and pandemic organisms as quickly as possible. The most accurate means of detecting these organisms is through identifying their unique DNA. Citing the need for one prioritized list of biothreat targets and standardized information on pandemic organisms, Bishop stressed the importance of partnering with government in coordination and communication.

LESSONS FROM HIV/AIDS

The first case of AIDS was reported in the United States in 1981. Since then there have been 900,000 cases reported in the U.S. and the disease has become a major international epidemic, accounting for some 25 million deaths worldwide. Today, HIV/AIDS is a far different disease than it was a decade ago. Originally considered to infect mainly gay men in the developed world, today it has taken firm root and is spreading in developing countries around the world, with a staggering 6,000 new infections per day.

The battle against HIV has produced some of the greatest innovations in the history of medicine, according to Howard Jaffe, M.D., President and Chairman of the Board of the Gilead Foundation. HIV/AIDS was first recognized and reported by the CDC in June 1981 with the first cases of pneumocystis pneumonia (PCP) in five gay men without known immunodeficiency in Los Angeles. In the 1980s, HIV infection was in effect a death

sentence. Thanks to rapid breakthroughs in scientific understanding of retroviruses, effective antivirals, used in combination regimens, have been created that allow patients to live for decades, transforming a fatal infection to a chronic manageable condition. Jaffe characterizes HIV/AIDS treatment today as undergoing a renaissance, not only with improved drug safety and effectiveness, but with combination drug formulations that make it easier for patients to take their daily medications. Decreased pill burden has positively affected adherence rate and treatment outcomes.

Jaffe stressed the importance of always being on the lookout for opportunities to innovate, through finding new ways for people who may not know they have the virus to get tested, and thereby decreasing infection rates. The U.S. Centers for Disease Control estimate that of

Four Lessons Learned From HIV/AIDS

1. Progress – with the exception of the advent of combination therapies – has been incremental.
2. Cooperation – among industry, academia, regulators, and activists – is essential.
3. Simplicity – with the goal of having a once-a-day, all-in-one pill – is a critical goal that has major public health consequences.
4. Complacency is dangerous.

the more than one million Americans infected with HIV, at least one-fourth are unaware of their infection. These individuals are the greatest source of ongoing HIV transmission. And, as they are unaware of their HIV status, they generally present to medical care with advanced AIDS and face morbidity and mortality similar to the patients first diagnosed in the early 1980s. In the United States, the ongoing HIV transmission and delayed HIV diagnoses must be a wake-up call for our public health system.

Noting that infection levels mirror poverty levels around the world, Jaffe lauded global efforts such as the Three by Five Initiative – launched in 2003 by the WHO and UNAIDS to treat 3 million HIV-infected individuals in developing countries by the end of 2005, as well as funding pledged by the President’s Emergency Plan for AIDS Relief (PEPFAR) to increase access to therapy in developing world countries. Although the WHO program to date has only treated close to half of the people (1.3 million) it set out to reach, it has helped counter the stigma associated with testing positive for HIV, and it has helped create and raise the standard of treatment infrastructure not only for HIV, but for other infectious diseases. PEPFAR also has enabled the Department of Health and Human Services to work closely with drug manufacturers to streamline the approval process for branded and generic fixed-dose combinations, and to co-package antiretrovirals.

In discussing Gilead’s role in HIV/AIDS treatment, Jaffe stressed both the company’s focus on innovation to create best-in-class medications, and its partnerships in Africa, Asia, and the Caribbean. Increasing scale in manufacturing and leveraging relationships with local manufacturers and/or governments has allowed Gilead to reduce costs and to provide drugs at no-profit pricing through the Gilead Access Program to many of the world’s least developed and hardest-hit countries. By simply altering packaging and the color of its pills for different countries, Gilead has made it clear that its medicines manufactured for distribution to other countries are not for re-importation to the U.S. Gilead also is involved in prevention studies, and has committed free drugs to clinical studies which not only treat infected individuals, but support the development of treatment infrastructure and define best practices in care.

The overarching lesson learned from HIV/AIDS, Jaffe said, was to “do the right thing for people. It is never good enough in industry to simply *not* be evil. In addressing this horrific epidemic, we have to take the extra step and be a good world citizen.” We can stem the tide of this epidemic by applying good public health principles of broader, more routine HIV testing, earlier treatment, and continuing support of research and innovation in the area of therapies and vaccines.

FDA TWIN GOALS: INCREASING SAFETY AND SPEEDING DELIVERY

The U.S. Food and Drug Administration (FDA) occupies a pivotal position in the effort to develop breakthroughs against infectious disease. Vaccines, antiviral drugs, diagnostic technologies – each requires extensive FDA review and approval in order to reach the patient market. Faced with public health crises, the agency has focused on accelerating review processes for breakthrough products. For example, it took five months – not the usual twelve – in 2004 for FDA to approve Truvada[®], Gilead’s two-drug combination of tenofovir and FTC to treat HIV/AIDS. “It is an example of how government leadership can result in patients getting more rapid access to important therapies,” said Gilead’s President and CEO and CHI Chairman John Martin, Ph.D.

“Focusing on safety does not necessarily slow the approval process. In fact, they are complementary goals.”

*– Scott Gottlieb, M.D.,
FDA Deputy Commissioner
for Medical and Scientific Affairs*

Gottlieb pointed to post-market data as critical to the efficient and effective translation of innovations into practical approaches to care. He listed several ways in which the FDA is using post-market data to both improve safety, and to expedite the process of bringing new innovations to market:

- For example, the FDA is working to improve reporting by clinicians of adverse events, as well as to improve epidemiological databases, and develop good practices for gleaned useful information from post-market data. The agency’s FY2007 budget calls for modernizing its Adverse Event Reports System (AERS) to provide for integration with Centers for Medicare and Medicaid Services (CMS) databases to enable FDA to gather more information from the point of care about potential safety problems.
- In addition, the FDA is placing more emphasis on improving risk communication – including giving the media better access to the agency and more time to both digest and communicate to the public complex medical and contextual information. The agency is collaborating more with medical societies in order to communicate more clearly and effectively with physicians, and will be using focus groups and surveys with physicians to gauge how improved risk communication is affecting their practices. The FDA will soon announce a new physician-labeling rule that will improve label readability. And it is considering creating kiosks in pharmacies to provide more accessible and more useful information to patients.
- Together with using post-market data to inform clinical development processes, the FDA is expediting innovation as it begins

to set new standards to measure responses to drugs and devices in preclinical and clinical studies. For example, it will be collaborating with a small start-up company to validate certain assays as measures of liver toxicity versus measuring liver toxicity in mice. It will soon be funding clinical trials that may validate the use of assays and PET scans to determine or measure pathology in certain cancers and neurodegenerative diseases. It is using microdosing to get earlier reads of drug metabolism and effects earlier in the development process. And it will be identifying public-private partnership opportunities to validate biomarkers as well as better trial design.

Gottlieb cautioned that adopting new approaches within the FDA will prompt risk-taking both within the agency and within the industry – which implies trust on both sides to use new information responsibly and well.

PLANNING AND RESPONSE ACTIVITIES – RESOURCES

On November 1, 2005, the U. S. Department of Health and Human Services (HHS) released the National Strategy for Pandemic Influenza. (The full document is available online at www.whitehouse.gov/homeland/pandemic-influenza.html). The U.S. is one of about 50 countries to have drawn up pandemic-preparedness plans. Only a handful of nations, including Britain and Canada – but not the United States – have given their plans legal status. Anthony

Fauci, M.D., Director of the National Institute of Allergy and Infectious Diseases, says the U.S. plan serves as “a blueprint to help states and local governments handle a pandemic,” but “there are challenges and problems that remain to be worked out.” According to infectious disease experts, stockpiles of anti-viral medications and flu vaccines are inadequate, and necessary vaccine surge capacity does not currently exist in the United States or in the world. Federal activities and initiatives include:

- **U.S. Department of Health and Human Services Pandemic Planning Update.** One-stop access to federal government avian and pandemic flu information. Among many resources are links to state and local planning agencies, regional and state summit conferences, maps showing nations with confirmed cases of H5N1 avian flu and patterns of bird migration. (www.pandemicflu.gov)
- **U.S. Centers for Disease Control and Prevention** offers a rich set of resources that cover avian and pandemic influenza as well as other public health threats: tuberculosis, HIV and bioterrorism. (www.cdc.gov)
- **World Health Organization Epidemic and Pandemic Alert and Response** website provides updated international information about incidents and news. (www.who.int/csr/disease/avian_influenza/en)
- **The California Department of Health Services (CDHS)** presents its draft preparedness plan along with links to municipal and county health agencies, basic information on

avian flu, and notices of meetings, conferences and publications. (www.dhs.ca.gov)

- **Nature**, a leading scientific journal, publishes an **Avian Flu Web Focus** that now contains an Internet ‘mashup’ (using Google Earth) that tracks the spread of the disease, in humans and birds, around the globe. The site also contains research articles and an outbreak timeline, alongside a comprehensive archive of news, features, communications and letters examining the threat of a new human flu pandemic in the near future, and what can be done to prevent it. (www.nature.com/nature/focus/avianflu/index.html)
- **Federal legislation (PL109-148)** was enacted in December 2005 to provide \$3.8 billion for state and local pandemic planning, vaccine development, and antiviral and supplies stockpiling. Also included was language providing liability protections for emergency drugs, vaccines and other countermeasures.
- In the spring of 2006, the federal pandemic plan will have approval from all government authorities.

History suggests that a pandemic is inevitable, yet we are far from prepared to battle global influenza and limit the damage it will cause. Our experience with infectious diseases over the past generation shows just how small our global village has become. Emerging infections leapfrog from one population center to another with terrible swiftness. Our task as physicians, researchers, public health officials, biotech leaders, educators, and legislators is to face these challenges by forming local, national, and international public/private partnerships. We must innovate in every aspect of health care by improving surveillance methods, diagnostics, antivirals, and vaccines. These actions will improve our ability to prevent and treat seasonal influenza. And seasonal preparedness translates into pandemic influenza preparedness. Being prepared for pandemic influenza will enhance our ability to meet other emerging global infectious diseases, the threat of bioterrorism, and to withstand disasters like Hurricane Katrina of 2005.

CHI – California Healthcare Institute represents more than 250 leading academic research, biotechnology, medical device, diagnostics, and pharmaceutical organizations in California. CHI’s mission is to advance responsible public policies that foster medical innovation and promote scientific discovery.



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