Avian Flu Readiness

Progress on Vaccines, Stall-Out on Logistics

by Christine Craig

In early May, the ABC fictional TV movie "Fatal Contact" was broadcast, about the arrival of an avian flu pandemic. With millions dying internationally, it placed the U.S. epicenter in Richmond, Virginia, showing gore and body-bags. Thousands of viewers had the same reaction as those in the 1930s did to the radio equivalent—H.G. Wells' "War of the Worlds"—when they thought it was for real.

Instead of terrorizing the public, or broadcasting nonspeak from Administration officials, what is sorely needed are updates on the science involved, and a real mobilization of infrastructure to handle the genuine threat.

Of note this month, are two key aspects of the situation: There is some motion on developing vaccine capabilities, though not nearly enough; and secondly, there is an extreme lack of logistics in depth, to deal with a mass-illness outbreak or disaster. Local county and city officials are clamoring for assistance.

We provide, here, updates in these areas, beginning with noting a new study of how an avian flu pandemic might play out in the United States.

Produce and Distribute

On May 3, the Department of Health and Human Services (HHS) came out with its updated Pandemic Influenza Implementation Plan, providing new data gathered from recent pandemic simulation studies done on the Los Alamos National Laboratories supercomputer, and using different parameters of the infectivity, or spreadability, of a pandemic influenza virus ("Mitigation Strategies for Pandemic Influenza in the United States," Timothy Germann et al.,*Proceedings of the National Academy of Sciences,* April 11, 2006). This study was funded by the Department of Homeland Security and the National Institute of General Medical Sciences.

Although the usefulness of such computer modelling in predicting real events is dubious, it is important to know that it is informing the actions of the National Institutes of Health, the Centers for Disease Control and Prevention, and other agencies charged with distributing funds for pandemic response.

The authors of the new study concluded, as expected: "We believe that a large stockpile of avian-based vaccine with potential pandemic influenza antigens, coupled with the capacity to rapidly make a better-matched vaccine based on human strains, would be the best strategy to mitigate pandemic influenza. *This effort needs to be coupled with a rapid vaccine distribution system capable of distributing at least 10 million vaccine doses per week to affected regions of the U.S.*" (emphasis added).

Thus, the tasks are restated: the necessity of having sufficient, effective vaccines; and the ability to distribute them. A massive and efficient vaccine production and distribution infrastructure is crucial to limiting the health and economic impacts of a pandemic to an attack rate of 10%, with a death rate of 2%—the goals of the HHS plan. (Two percent mortality, the most optimistic assessment of the 1918 pandemic, would still mean almost 6 million deaths in the United States!)

Vaccine Development Actions

The release of the results of the modelling study was followed closely by the release of an additional $1 billion by HHS for cell-based pandemic vaccine development by five companies: GlaxoSmithKline ($274.75 million), MedImmune ($169.46 million), Nortis Vaccines & Diagnostics ($220.51 million), DynPort Vaccine ($40.97 million), and Solvay Pharmaceuticals ($298.59 million). Sanofi Pasteur had previously been awarded $97 million in 2005 for development of cell-based production. (A previous round of funding in 2005 gave substantial funding to several companies to move egg-based vaccines into clinical trials).

HHS secretary Mike Leavitt commented, as he announced the new funding: "Our current capacity of egg-based influenza vaccine production is not sufficient to meet increased demands during an emergency. Accelerating the development of this vaccine technology, and creating domestic capacity, are critical to our preparedness efforts."

Cell-based vaccines are those which do not need to be manufactured in chicken eggs. They are often grown in canine kidney cells in industrial bioreactors, a process which can potentially produce more pandemic vaccine much more quickly than incubating live virus in millions of fertile eggs. HHS has estimated that producing 300 million doses of vaccine would require 900 million chicken eggs, which might be hard to get if a poultry pandemic preceded the human one. Large volumes of the cells can be pre-grown and frozen until needed, then unfrozen and infected with the vaccine virus. After amplification in cell culture, the vaccine virus would be harvested to produce the killed, attenuated, or protein-product viral vaccine.

Newer technologies are in the pipeline, and have been given small grants for research and development, but have not yet been fully funded for production. It is hoped that the next round of funding will award more funds to some of these newer, promising technologies, such as DNA vaccines and novel vector vaccines—using viruses like adenovirus (cold

virus) or baculovirus (insect virus) to carry pandemic flu proteins.

Two vaccines will be necessary—a contingency taken into account somewhat in the new Los Alamos computer simulation study of pandemic outbreak. The first would be made *before* a pandemic, using a stockpile made from already circulating pre-pandemic viral strains. This would be used for the first massive pandemic vaccinations, At the same time, virus from the actual human infections of the pandemic strain, would need to be used, to rapidly manufacture the actual *pandemic* vaccine; this would be distributed as soon as available.

The prime scenario would be to get the matched vaccine into distribution within the critical two-week period identified in the modelling simulation, if possible.

The HHS stated goal, however, is still only to get the pandemic vaccine into distribution within six months after an outbreak. By that time, most of the recipients would probably be survivors of the pandemic flu.

Thus, two things become clear: The first, is that by far the most important vaccine will be the pre-pandemic vaccine. The better, faster, and more cross-reactive that vaccine is, the more people will survive (not necessarily avoid) the disease.

Public Health Logistics Lacking

The second, is that the vaccine technology that the HHS has so far pumped money into, does not fit the bill. Even the cell-based technology funded to date is old, clunky, slow, and inflexible. What are needed are vaccines engineered with modern recombinant DNA technology, using highly immunogenic systems of conserved viral proteins (proteins very similar in many flu strains) and effective adjuvants (chemicals which boost immune response to antigens in the body). Such vaccines could be made cheaply ahead of time, stored indefinitely, and used against many flu types in a pinch.

Thus, while the flow of funding has indicated a serious interest on the part of Congress and the Administration to ramp up new and effective vaccine production strategies, much more must be done, and still, the weakest point of the current readiness plans, is the distribution networks. The United States is hampered even in yearly seasonal flu vaccine distribution, by the mishmash of public and private supply chains and breakdowns.

On May 22, representatives of the National Association of County and City Health Officials (NACCHO) were in Washington, D.C. begging for resources for equipment and anti-viral stockpiles to implement local pandemic plans around the country.

As the executive director of NACCHO, Patrick Libbey, commented during his press meeting, "I think we need to look seriously at matching the development of vaccines and antivirals, with the means of making sure they can be distributed." If the vaccines don't get to the people's arms, they do no good. Although Mike Leavitt has repeatedly insisted that local responders will be on their own in a pandemic, money for implementing the local response has been slow in coming, leaving the already strapped cities and counties with lots of great plans, but few tools and supplies to carry out the plans.

Computer Modelling

The new pandemic computer modelling—with all its drawbacks—has brought greater definition to some of the previously "fuzzy" areas in planning, making it all the more clear, that resources must be mobilized. For instance, given limited courses of Tamiflu available, how should the emergency stockpiles of antivirals be prioritized? Is it best to give them to first responders, saturate an outbreak area with them, or target them to those close to infected people within an outbreak area (targetted antiviral prophylaxis)?

Although the Federal agencies are not yet making public their prioritizing plans, the focus of their study, on targetted application of antivirals, suggests that it might be used, although it is the most arduous plan to implement.

The modelling study found that, for a virus of lowest infectivity, current stockpiles (around 5 million courses) of an effective antiviral would be extremely valuable in achieving the target success goal of limiting viral attack rate to around 10% of the population. With a highly spreadable virus, however, the courses needed to be effective would exceed our ability to stockpile enough. And lesser amounts proved relatively useless in damping down a pandemic of high infective potential.

As many already would suspect, an adequate supply of a pandemic vaccine was found to be the most important single element in lessening morbidity and mortality, but not the length, of a pandemic.

This measure was most effective, under modelling parameters which assumed a limited amount of vaccine—if everyone possible were given just a first dose, of even a less-than-perfectly-matched vaccine, during the first two weeks of a pandemic, rather than vaccinating fewer members of the population, but with two doses. The key was to vaccinate massively and early in the outbreak.

Of course, the use of multiple strategies simultaneously—social distancing and isolation strategies, targetted antiviral distribution, and massive vaccination—was the most effective course of action to limit the pandemic.