Feds Spell Out Plan for Dealing With Flu Pandemic

Draft of federal plan calls for stockpiling vaccines and developing antiviral drugs and prophylaxis.

BY DAVID STERNBERG
Contributing Writer

BALTIMORE — Acknowledging that "flu has a huge news factor," Bruce Gellin, M.D., spelled out the federal influenza pandemic preparedness plan at a biodefense research meeting sponsored by the American Society for Microbiology.

The Department of Health and Human Services' draft Pandemic Influenza Response and Preparedness Plan, developed in August 2004, includes influenza control, stockpiling vaccines, developing antiviral drugs and prophylaxis, providing quality medical care, and maintaining community services, said Dr. Gellin, director of the National Vaccine Program Office, a division of HHS. The World Health Organization originally developed pandemic preparedness guidelines in 1999 for other organizations to follow.

"There are a lot of unknowns," said Dr. Gellin. "When will a pandemic occur? How bad will it be? And will there be major social and economic fallout? We need to continue to identify unmet questions."

Improving vaccine preparedness is a major focus of the HHS plan. To that end, Dr. Gellin said the United States must enhance annual influenza vaccine use, ensure a year-round egg supply, increase and diversify U.S. manufacturing capacity, and improve the ability to rapidly develop reference strains.

As for antiviral drugs, the U.S. government currently stockpiles 2 million doses of Tamiflu (oseltamivir) and 4 million doses of Flumadine (rimantadine). He acknowledged the need for a greater stockpile of these drugs, as well as a push for other therapies besides antivirals.

Even in the case of a mild pandemic, Dr. Gellin emphasized the heightened need for inpatient medical services and effective triaging of patients, noting that there would be an estimated 25% increase in demand for inpatient beds, ICU beds, and ventilators.

A few key issues remain unresolved, according to Dr. Gellin, including determining priority groups for early vaccine and antiviral use in the event of a pandemic; purchase and distribution of public- and private-sector vaccinations; and legal issues, including indemnification, liability protection, and compensation.

Two other significant issues addressed in the pandemic plan are development of new vaccines and therapeutics.

Richard J. Webby, Ph.D., of St. Jude Children's Hospital in Memphis, pointed out the many considerations for creating a vaccine in response to an emerging influenza pandemic.

"There is no way of accurately predicting what strain it might be; there is enormous diversity of viruses in animal reservoirs, and some viruses are highly pathogenic," he said.

Unresolved issues include determining priority groups for early vaccine and antiviral use in a pandemic, and purchasing public- and private-sector vaccinations.

But a procedure called reverse genetics has been significant in Dr. Webby's work at St. Jude's in accelerating the development of vaccines. Reverse genetics begins with a cloned segment of DNA and introduces programmed mutations back into the genome to investigate gene and protein function.

"Reverse genetics is likely to play a key role in future inactivated and attenuated vaccine strategies," said Dr. Webby.

As for antivirals, the existing therapeutics are M2 ion channel inhibitors and neuraminidase inhibitors (NAIs), said Simon P. Tucker, Ph.D., of Biota Holdings Ltd., in Melbourne, Australia.

The M2s are Symmetrel (amantadine) and Flumadine, both of which are dosed at 100 mg twice a day. The NAIs are Relenza (zanamivir) and Tamiflu. Relenza is dosed at 10 mg twice daily and Tamiflu at 75 mg twice daily, said Dr. Tucker.

There are some basic differences between the two drug classes, Dr. Tucker said. M2s are used only for influenza A and have a high clinical resistance; NAIs are effective against both influenza A and B and have a low clinical resistance. For these reasons, NAIs, particularly Tamiflu, are prescribed more often than M2s. Most prescriptions are written by family physicians; most of the patients are aged 20-59 years.

Dr. Tucker noted that another drug class is under development—long-acting neuraminidase inhibitors (LANIs)—and has exhibited some early success.

One LANI monomer (R-118958) has shown to be more potent and more effective than Relenza, said Dr. Tucker. He noted a few of the advantages to LANIs: one-time-only therapy, once-weekly prophylaxis, and an optimal use for interpandemic cases.

Biota Holdings Ltd. was involved in the development of Relenza and is currently developing LANIs under a contract from the National Institutes of Health. ■

Many High-Risk Patients Got Flu Shots

BY ALICIA AULT
Contributing Writer

WASHINGTON — Despite the severe shortage of influenza vaccine this winter, the elderly, young children, and others at risk were able to find and receive shots, officials said at the National Immunization Conference sponsored by the Centers for Disease Control and Prevention.

Once it was known last October that Chiron Corp. would not be able to deliver its half of the nation's vaccine supply, the CDC immediately set up a special surveillance team to track where the vaccine was going and who received it, said Susan Chu, Ph.D., acting director of the agency's Office of Science Policy and Technology Transfer.

Seventeen new questions on the flu vaccine were added to the monthly Behavioral Risk Factor Surveillance System survey. From November 2004 to February 2005, 105,473 adults and 35,106 children (by proxy) were interviewed, said Michael Link, Ph.D., of the CDC's behavioral survey branch.

And, in a change of pace designed to keep state and federal agencies on top of the shortage, data were submitted to CDC weekly, not monthly, and were analyzed within days, giving states new data every 12 days or so, Dr. Link said.

As of late March, the survey found that vaccines were received by 63.5% of respondents over aged 65 years, 26% of 18- to 64-year-olds at high risk, and 36% of health care workers, said Gary Euler, Dr.P.H., of the CDC National Immunization Program's epidemiology and surveillance division. These figures were slightly higher than those gathered through January and reported in the CDC's Morbidity and Mortality Weekly Report. According to that data, 62.7% of those over aged 65 years, 25.5% of those with high-risk conditions aged 18-64 years, and 35.7% of health care workers received vaccinations (MMWR 2005;54:304-7).

Through February, among healthy Americans, 7.2% of those aged 18-49 years, and 17.3% of those 50-64 years said they had been vaccinated, compared with 6.9% and 16.5%, respectively, through January.

Fifty-two percent of children aged 6-23 months received a vaccine (up from 48.4% through January), a high uptake rate, given that 2004 was the first year the CDC's Advisory Committee on Immunization Practices recommended adding the flu shot to routine immunizations, said Carolyn Bridges, M.D., an epidemiologist with the agency's influenza branch.

Dr. Euler said there was room for improvement, as the survey found that many parents said they did not get vaccines for their children because they did not think they needed them.

The demand for vaccine among patients aged 65 years and older was mostly met, though there was some problem getting vaccine in early November, Dr. Euler said.

An audience member questioned whether some of the demand had been met in Canada. As part of the survey, patients were asked where they got a vaccine. So if they went to Canada, that data would be captured, though it has not been analyzed yet, Dr. Euler said.

Vaccination rates also varied from state to state. Preliminary data indicate that states with lower immunization coverage had a smaller vaccine supply. Further analysis of the variation and the entire flu database will be coming over the next 6 months, Dr. Link said.

The CDC researchers acknowledged that the survey was limited because it is self-reported information, and does not cover people who are institutionalized.

Dr. Bridges said the CDC currently is researching whether faster analysis of flu data helped states with their shot distribution and management. ■

HHS Hopes to Speed Production of Pandemic Vaccine With Contract

The U.S. Department of Health and Human Services recently awarded $97 million to Sanofi Pasteur to speed development of a manufacturing technique that could cut the time it takes to get an influenza vaccine to market. But the technique, which involves growing flu strains in cell culture, initially will be used only to create a vaccine against a pandemic strain.

Traditionally, vaccine production takes at least 9 months, from the time strains are selected for inclusion to when the shot is ready for distribution. The new technique might cut a few weeks off that process, with most of the savings coming in the beginning.

Under the current manufacturing scenario, influenza strains must be adapted so they can be grown in chicken eggs. Delays come when the strains either cannot be grown in eggs, or are difficult to grow. With the new technique, the strain would not need adaptation because it would be grown in a human cell line. The line—of retinal cells—was developed by a Sanofi partner, Crucell, a Dutch biotechnology company.

Even though many experts think the cell culture will be more reliable than eggs for growing influenza vaccine strains, there is no guarantee. And even if the manufacturing technique is successful, it will still have to be approved by the Food and Drug Administration.

Sanofi Pasteur said it anticipates beginning human trials late next year. The HHS contract provides funds only for phase I and II studies, but the company anticipates continuing through phase III and on to market.

As part of the HHS contract, the company is also required to complete a feasibility study for supplying up to 300 million doses a year. Currently, the company has no plans for building a manufacturing facility that could accommodate that production.

—Alicia Ault