New Methods Could Speed Flu Vaccine Production

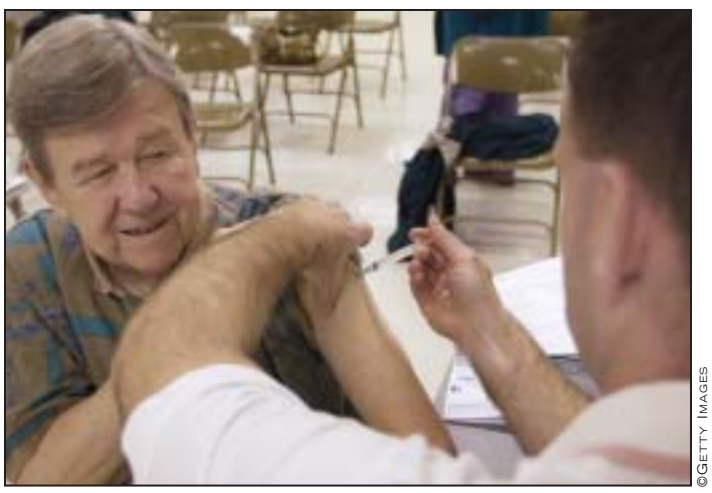
BY JEFF EVANS
Senior Writer

WASHINGTON — Methods are now available to produce influenza virus vaccines in a greater number of doses and with more up-to-date coverage of relevant strains than what is currently available, Peter Palese, Ph.D., said at a biodefense research meeting sponsored by the American Society for Microbiology.

In most instances, these methods can be applied to both killed (inactivated) and live (attenuated) vaccines, said Dr. Palese, chair of microbiology at Mount Sinai Medical Center, New York.

Viruses in killed vaccines are grown in embryonated eggs, purified, inactivated with formaldehyde, and usually then treated with a detergent to make the vaccine less pyrogenic. The recently approved live vaccines are grown in tissue culture at a lower temperature (25° C) and in embryonated eggs. This makes the virus temperature-sensitive and attenuated, limiting the virus to a few replication cycles in the upper respiratory tract.

New adjuvants should help reduce the amount of antigenic viral material in each vaccine dose that is needed to induce protective immunity, he said. With adjuvants, the antigenic mass in each dose could be reduced to anywhere from a fifth to a tenth of its current amount. Alum is the only adjuvant approved by the Food and Drug Administration for use in combination with some vaccines.



©GETTY IMAGES

With adjuvants, the antigenic mass in each vaccine dose could be reduced to 10%-20% of its current amount.

"This is an area where we really have to improve," he said.

Each February, the FDA decides which strains should be included in vaccines for the next influenza season. Only the viruses that are circulating until the end of January can be considered in the decision. The FDA would make better decisions about which influenza isolates should be included in the vaccine if the decision could be delayed until May or June, Dr. Palese said.

Vaccines for the 2005-2006 season were trivalent with surface antigens from an influenza A H3N2 isolate from 2004, an older influenza A H1N1 isolate from 1999, and an influenza B isolate from 2002. One or two of the three components changes each flu season, Dr. Palese noted.

A new technique may let researchers adjust the viral antigens in vaccines and produce vaccines more quickly. It would work by inserting a combination of DNA copies of specific genes from a laboratory viral strain and genes for the hemagglutinin and neuraminidase antigens on currently circulating viruses into cells in a tissue culture. The resulting recombinant seed viruses could then be generated within 1 to 2 weeks for distribution to manufacturers for annual vaccine production.

This process allows more time to select the appropriate antigenic seed strains, he said.

Vaccine developers also may be able to use this process to engineer the influenza virus genome to express an altered version of nonstructural protein 1 (NS1). NS1 normally inhibits the interferon response of a host cell; viruses that lack NS1 cannot block interferon and, as a result, cannot replicate. Viruses with a truncated version of NS1 are still able to replicate, although not as easily as those with normal NS1, because the truncated protein induces an interferon response from the host cell. Viruses with truncated NS1 are attenuated and have been shown to immunize mice against challenges with high doses of active virus.

The viruses with truncated NS1 are highly immunogenic because interferon acts as an adjuvant by enhancing the production of immunoglobulins and contributing to the activation of dendritic cells required for antigen presentation. The robust immune response to these viruses could make it possible to scale down the amount of infectious agents in each dose by several orders of magnitude; many more doses could be manufactured in this way, Dr. Palese said. ■

FDA Panel Responds to WHO Flu Vaccine Recommendations

BY DEEANNA FRANKLIN
Associate Editor

BETHESDA, MD. — A federal advisory panel unanimously voted to change two of the three strains slated to compose the 2006-2007 influenza vaccine.

The Food and Drug Administration's Vaccines and Related Biological Products Advisory Committee recommended the changes based on shifts in viral activity, based on data culled from surveillance sites in Japan, England, Australia, and the United States.

The recommended vaccine changes correlate with the World Health Organization's suggested vaccine composition for the Northern Hemisphere for the 2006-2007 winter season.

The advisory panel recommended that the trivalent vaccine retain the influenza A(H1N1) strain—A/New Caledonia/20/99(H1N1)-like strain—due to evidence of continued resilience.

But the panel suggested replacing the A/California/7/2004(H3N2)-like virus with A/Wisconsin/67/2005(H3N2)-like virus. Also, the influenza B/Shanghai/361/2002-like virus should be replaced by the B/Malaysia/2506/2004-like virus.

According to Dr. Zhiping Ye, senior investigator of the division of viral products at the FDA's Center for Biologics Evaluation and Research, influenza A infections were inadequately covered by the 2005-2006 vaccine. It's estimated that in the pediatric population there was an overall 50% reduction in the hemagglutination inhibition (HI) reaction to the H3N2 component of the vaccine.

A similar reduction in coverage of the A/Wisconsin strain was noted in adult populations in Europe, Japan, and the United States.

"If we use Wisconsin as a vaccine, then we probably will get better coverage," Dr. Ye said. "But this is only one piece of the puzzle." Surveillance studies show that several other strains in the same lineage as A/Wisconsin also were inadequately covered by the current vaccine. However, there would likely be residual coverage of these strains by targeting the A/Wisconsin strain.

The current vaccine still appeared effective against the influenza A (H1N1) strain, A/New Caledonia/20/99(H1N1)-like virus, according to data from surveillance sites in North America, South America, Europe, Asia, Africa, and Australia.

Data from the United States and Europe showed that several strains were inadequately covered by the influenza B component of the current vaccine, and the B/Malaysia/2506/2004-like virus was one of them, Dr. Ye noted.

The vote on the 2006-2007 vaccine composition was unanimous, but the panel members had some reservations.

Although influenza A strains are responsible for most U.S. influenza cases, in recent years the selection of an influenza B strain has been more difficult to accurately pin down. "This winter the B/Victoria has been dominant in North America, but our vaccine was the B/Yamagata strain," said panelist Dr. Robert B. Couch, professor of medicine, microbiology, and immunology at Baylor College of Medicine, Houston.

"We do the best we can to predict the likely epidemic virus, but for roughly the last 3 years, it's been a little too much of a guess with the influenza B. If it's going to continue this way, then we need to discuss how to address this problem," Dr. Couch said in an interview.

Despite these misgivings, he voted in favor of the B/Malaysia strain, which is part of the B/Victoria/2/87 lineage. The B/Shanghai/361/2002-like virus in the current vaccine is a part of the B/Yamagata/16/88 lineage, which, despite last year's predictions, did not become the dominant virus for the 2005-2006 flu season.

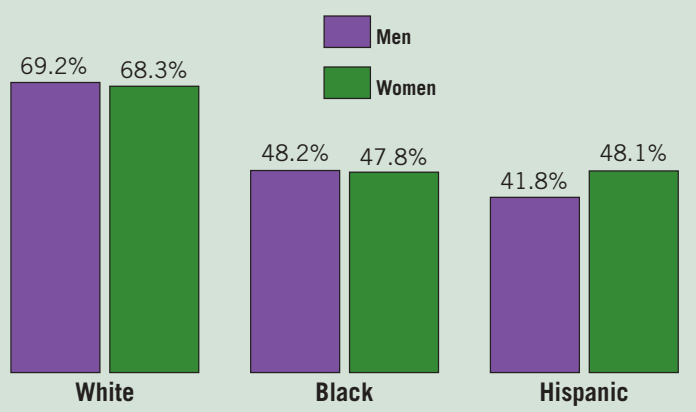
In response to Dr. Couch's admonitions, the panel urged the FDA to convene a workshop to address future use of a quadrivalent vaccine with two influenza B components.

"There is less of an issue about a second B component this year than there has been in previous years. Last year we had a particularly difficult time in deciding on a B component, however, the issue … will continue to arise" and should be dealt with by the proposed workshop, said Dr. Ruth Karron, committee chair and professor of international health at the Johns Hopkins Bloomberg School of Public Health, Baltimore.

Albert Thomas, director of viral manufacturing at Sanofi-Pasteur, noted that in the interest of building an adequate supply, vaccine production at the France-based company had already begun with the influenza A (H1N1) strain A/New Caledonia/20/99(N1H1)-like virus prior to a formal recommendation by the WHO and the FDA. Distribution of Sanofi Pasteur's vaccine is scheduled for late August 2006. ■

DATA WATCH

Percentage of People Aged 65 Years and Older Who Had Received a Flu Vaccine in the Preceding Year



Note: Based on a 2003 national study of 5,538 adults.
Source: Centers for Disease Control and Prevention

ELSEVIER GLOBAL MEDICAL NEWS