FDA Panel Favorable Toward Quad Flu Vaccine

BY ELIZABETH MECHCATIE

SILVER SPRING, MD. — The idea of adding a second influenza type B strain to the seasonal influenza vaccine was met with generally positive responses by vaccine experts who discussed the utility of a quadrivalent vaccine at a meeting convened by the Food and Drug Administration.

The FDA's Vaccines and Related Biological Products Advisory Committee discussed the pros and cons of adding a second B component to the vaccine, but it did not vote on the issue or make any formal recommendations to the FDA.

Since 2000, the two cocirculating lineages of influenza B viruses (B/Yamaguchi and B/Victoria) have become more antigenically distinct, raising the issue of whether adding a second B strain to the seasonal flu vaccine would have a positive public health benefit, Rakesh Pandey, Ph.D., of the FDA's Division of Vaccines and Related Products Applications, said at the meeting.

'If we go to the trouble of immunizing against' two influenza A strains, 'then we should have a vaccine with coverage against both B strains.'

Cocirculation of the two B lineages means that "some degree of mismatch between a vaccine and circulating strain is inevitable," which can reduce the effectiveness of the trivalent vaccine as well as public confidence in the vaccine, pointed out Carrie Reed, D.Sc., of the Centers for Disease Control and Prevention, who also spoke at the meeting.

The current trivalent seasonal flu vaccine includes two influenza A strains (H1N1 and H3N2) and a B strain.

Among the issues that need to be considered before a second B strain is added include the clinical data needed to establish the safety and immunogenicity of a vaccine with two B strains; the public health impact and cost; and whether better coverage of influenza B would make up for potential delays in manufacturing and vaccine availability, according to Dr. Pandey. Another issue is whether the quadrivalent vaccine could be targeted to subpopulations, such as children and the elderly.

B strains are harder to grow than A strains, which could delay the availability of the influenza vaccine. However, the manufacturing capacity of influenza vaccine has markedly increased over the past 4-5 years, so manufacturers may be able to adjust to adding another component to the vaccine, Dr. Pandey noted.

Dr. Reed presented the results of a CDC analysis, conducted at the request of the FDA, on the impact that a second B strain would have had on the last 10 flu seasons in the United States. The analysis used a model that averaged all ages, and calculated the burden of influenza during each season by type, subtype, and lineage. The model did not include cost estimates.

Considering that B viruses do not grow as well as A viruses, about 25% less vaccine would be produced if a second B component were added to the vaccine, she said. This could have a negative impact on seasons in which supply of the influenza vaccine is similar to the demand, but for seasons in which supply exceeds the demand, the amount of quadrivalent vaccine available would still exceed the amount of vaccine administered, she pointed out.

For example, during the 2007-2008 influenza season, type B strains accounted for 29% of the virus tested, and 98% of the B strains tested were not the lineage included in that season's vaccine. Based on these data, the CDC analysis estimated that there would have been more than 1 million fewer cases of influenza, almost 7,500 fewer influenza-related hospitalizations, and about 320 fewer deaths if a quadrivalent vaccine had been available, Dr. Reed said. There was an excess supply of vaccine that season, so the lower number of vaccine produced would not have had a negative impact on coverage, she added.

During 2005-2006, about 20% of the circulating strains were influenza B viruses, and 78% of the strains were not the lineage in the vaccine. There would have been fewer doses of a quadrivalent vaccine, so an estimated 8% fewer people would have been vaccinated. Because of a better match provided by a quadrivalent vaccine, there would be an estimated 440,841 fewer cases because of the better match, but 298,204 more cases because of less coverage—a net benefit of 142,637 fewer cases, she said.

But for a season like 2004-2005, when there were problems with manufacturing that affected the supply and when the supply was similar to the demand, an estimated 15% fewer people would have been vaccinated if the vaccine had been a quadrivalent one. That season, 25% of the circulating strains were type B, and 26% of those B strains were the lineage not included in the vaccine. Considering these data and the supply issue, there would have been an estimated net increase of 151,566 cases of influenza if a quadrivalent vaccine had been used, according to Dr. Reed.

Several panelists said that information on the cost-benefit of a quadrivalent vaccine was crucial, because increased cost could affect immunization rates. Dr. Reed acknowledged the limitations of the model used in the CDC's analysis, which focused on the public health impact of a quadrivalent vaccine and did not include an analysis on the cost-benefit, did not consider potential adverse events associated with adding a second B component, and did not analyze different age groups separately, data that other panelists agreed were needed.

Several panelists also referred to the limited data on the effectiveness of the B component of the influenza vaccine. Because there are "very, very few pure" influenza B years, "we get used to equating influenza B effectiveness with what we know about influenza A effectiveness … but that may be totally erroneous," said panelist Dr. Theodore Eickhoff, professor emeritus in the division of infectious diseases, University of Colorado Health Sciences Center, Aurora.

Referring to the two cocirculating B virus lineages over the past few seasons, Dr. Roland Levandowski, an infectious disease specialist in Bethesda, Md., remarked, "If we go to the trouble of immunizing against" two influenza A strains, "then we should have a vaccine with coverage against both B strains."

At the close of the meeting, the panel chair, Dr. John Modlin, professor of pediatrics at Dartmouth-Hitchcock Medical Center, Lebanon, N.H., summarized the attitude of the panel regarding the prospect of a quadrivalent vaccine as "a qualified thumbs-up."

A model that incorporates age-specific influenza rates, morbidity, and other factors for determining the public health impact of a quadrivalent vaccine is clearly needed, Dr. Modlin said. "Hopefully, the committee has sent the message it would like to see the CDC model work continued," he added. ■

HPV Vaccine Does Not Seem to Increase Guillain-Barré Risk

BY KERRI WACHTER

The human papillomavirus vaccine does not appear to increase the risk of developing Guillain-Barré syndrome, despite isolated reports of the condition following vaccination, a study shows.

"I found that there's some overlap between the incidence of Guillain-Barré in the general population and Guillain-Barré after vaccination with Gardasil," Dr. Nizar Souayah said in an interview. However, he and his colleagues have not found Guillain-Barré to occur more often among those who have received the HPV vaccine than among people in the general population.

Dr. Souayah will be presenting the study at the American Academy of Neurology annual meeting in Seattle, April 25–May 2. The data were released early.

The Food and Drug Administration approved the vaccine in 2006 for use in girls and women aged 9-26 years to prevent infection against HPV strains 16 and 18, which cause most cervical cancers, and strains 6 and 11, which are responsible for most genital warts in the United States. Since the approval of Gardasil, more than 16 million doses have been given. There have been isolated reports of Guillain-Barré syndrome (GBS) after receiving the vaccine.

The estimated incidence of GBS after vaccination is 7 cases per million vaccinations, and for the general population is 4-10 cases per million individuals.

Dr. Souayah and his colleagues used data from the Vaccine Adverse Event Reporting System, which is a cooperative program for vaccine safety of the Centers for Disease Control and Prevention and the FDA. The system is a postmarketing safety surveillance program that collects information about adverse events that occur after the administration of U.S.-licensed vaccines.

Dr. Souayah searched the database using several key words: "numbness," "tingling," "Guillain," "Barré," and "Guillain-Barré syndrome." He identified roughly 350 patients. He then reviewed the data for each of these patients and characterized them as highly likely to have GBS, highly unlikely to have GBS, and unclear. He and his colleagues included in this analysis only those patients considered to be highly likely to have GBS.

They found 36 reported cases of GBS after vaccination with the HPV vaccine in 2006-2008. The mean age was 17 years. The estimated incidence of GBS after vaccination is 7 cases per million vaccinations. In comparison, the estimated incidence for the general population is 4-10 cases per million individuals.

"The most striking data [are] that most of the Guillain-Barré syndrome cases occurred within 6 weeks of vaccination," said Dr. Souayah, of the departments of neurology and neurosciences at the University of Medicine and Dentistry of New Jersey, Newark. The onset of GBS occurred within 6 weeks of vaccination in 75% of the individuals for whom the vaccination date was known.

"Our results show that Guillain-Barré is not occurring more often after HPV vaccination than it does in the general population. However, the fact that most of these cases occurred within 6 weeks of vaccination does warrant careful monitoring for any additional cases and continued analysis," he said in a statement.

He urged caution in interpreting the results. The database may not contain all cases of GBS after administration of the HPV vaccine; alternately, the database might contain cases that were not confirmed. "I would like to emphasize that we need more research," he said. ■