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Gardasil, Cervarix: Not Interchangeable

BY MICHAEL E. PICHICHERO, M.D.

With the licensure of GlaxoSmithKline's human papillomavirus vaccine Cervarix in October, we will soon have two vaccines that prevent cervical cancer in women. But they're not interchangeable, and this could lead to problems.

Cervarix is expected to join Merck's Gardasil on the U.S. market in February 2010. For the first time ever in vaccine history, we will have a situation in which two competing vaccines have very different components and adjuvants that could complicate the decision for practicing physicians—as well as insurers and buying groups—regarding which one to use. I think we need to view human papillomavirus (HPV) vaccines as exceptions to the usual rules of "equivalent and interchangeable" and consider stocking both. Parents should be informed of the features of each vaccine, and the decision to use one or the other should be made with informed consent.

Most clinicians know that both vaccines protect against HPV serotypes 16 and 18, the dominant causes of cervical cancer. But Gardasil also protects against HPV-6 and -11, primarily associated with genital warts, and has recently received approval for use in males, which Cervarix has not. But other differences between the two vaccines are less well recognized, and I believe will turn out to be important.

Although both vaccines are manufactured with similar technology using viruslike particles, Cervarix contains a novel adjuvant, ASO4, that is believed to be responsible for its ability to generate a greater antibody response to HPV-16 and -18, compared with Gardasil. According to a head-to-head comparison conducted by GSK, geometric mean titers of serum neutralizing antibodies ranged from 2.3- to 4.8-fold higher for HPV-16 and 6.8- to 9.1-fold higher for HPV-18 after vaccination with Cervarix, compared with Gardasil, across all ages (Hum. Vaccin. 2009;5:-705-19).

Although not proven, we might infer from those data that Cervarix might provide longer-lasting protection against HPV serotypes 16 and 18 and, therefore, a longer duration of time before a booster is needed. Both companies are studying duration of protection with their respective vaccines, and a just-published study showed sustained efficacy and immunogenicity of Cervarix up to 6.4 years (Lancet 2009 Dec. 3 [doi:10.1016/S0140-6736(09)61567-1]). For both vaccines, we should have answers before current vaccinees begin to lose protection.

'I think we all should stock both in our practices, and explain the differences to parents. ... This is going to be complicated.'

Both vaccines are indicated for the prevention of cervical cancer and cervical intraepithelial neoplasia (CIN) grades 1-3 due to HPV-16 and -18, and cervical adenocarcinoma in situ. However, Gardasil also has indications for the prevention of vulvar and vaginal intraepithelial neoplasias, which Cervarix does not.

Although not specifically mentioned in Gardasil's label (www.merck.com/product/usa/pi_circulars/g/gardasil/gardasil_pi.pdf), there is evidence that HPV strains 6 and 11, while not associated with cervical cancer, are responsible for 8%-10% of cases of CIN 1 (mild atypia). These lesions typically resolve, and guidelines from the American College of Obstetricians and Gynecologists do not recommend intervention beyond monitoring after CIN 1 is recognized, with the intent to intervene only if the lesion progresses to CIN 2. However, in practice women often request that the lesions be removed, and their gynecologists often do so, thereby incurring excess time, money, and some risk. Gardasil could potentially reduce a significant number of those procedures.

Meanwhile, data included in the label for Cervarix (http://us.gsk.com/products/assets/us_cervarix.pdf) show that it provides cross-protection against the carcinogenic HPV strain 31, which is responsible for a small yet significant proportion of cervical cancer cases. In one landmark study, serotype 31 accounted for 3.4% of squamous cell cancers in 1,739 patients (N. Engl. J. Med. 2003;348:518-27). Gardasil's label, in contrast, states that it has not demonstrated cross-protection against diseases caused by HPV strains not included in the vaccine.

These differences may seem slight, but consider a case in which a young woman who received Gardasil later develops a case of cervical cancer due to HPV-31. Might she be quite upset that she wasn't informed that there was another vaccine that could have prevented it? Conversely, a male or female patient given Cervarix later develops genital warts, or a female develops cervical atypia associated with HPV-6 or -11. Might these patients similarly feel that they were denied the chance to have prevented those outcomes?

Who decides which vaccine is used? In managed care settings, the decision is often made based on cost when vaccines are equivalent, but what about the HPV vaccines where the products are not equivalent?

The same goes for the manufacturer-run vaccine buying groups that offer discounts to increasing numbers of participating physicians who sign contracts that impose strict limits on the amount of vaccine that can be purchased outside of the specified brands.

This has not happened before with vaccines: The two competing brands are not interchangeable. I believe that health plans and vaccine buying groups need to recognize these factors and grant an exception to HPV vaccines.

I think we all should stock both vaccines in our practices, and explain the differences to parents. I plan to distribute pamphlets to patients and families and let them choose, with signatures confirming informed consent. I serve as a consultant to both GSK and Merck & Co. and have shared this information with both companies.

This is going to be complicated. ■

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Chikungunya Fever: Could an Outbreak Happen Here?

BY BRUCE JANCIN

VAIL, COLO. — Chikungunya fever is a tropical disease few American physicians are familiar with, but that could change quite suddenly, as physicians in temperate Northern Italy discovered to their great surprise two summers ago.

This mosquito-borne disease marked by sudden high fever, arthralgia and myalgia, prominent skin rash, and headache occurs in sub-Saharan Africa and Asia. At least, that was true until August 2007, when an outbreak of 254 cases—one fatal—struck out of the blue in the Ravenna province of Northeastern Italy.

What happened?

The traditional vector of Chikungunya virus is the *Aedes aegypti* mosquito. But when the virus underwent a mutation in a gene coding for a viral envelope protein, the mutant strain became at least 100-fold more infective for the *A. albopictus* mosquito, also known as the Asian tiger mosquito. The virus essentially jumped aboard a more competent vector.

Indeed, transmission by *A. albopictus* was responsible for a 2005-2006 outbreak of 500,000 cases of Chikungunya fever in the Reunion Islands off the Eastern coast of Africa. The outbreak then spread to India and Sri Lanka, where it caused more than 1.3 million cases, Dr. Kenneth L. Tyler explained at a conference on pediatric infectious diseases sponsored by the Children's Hospital, Denver.

"This would all be sort of a weird and remarkable event occurring in an out-of-the-way part of the world if it weren't for a cautionary development in Italy," added Dr. Tyler, professor of neurology, medicine, and microbiology at the University of Colorado at Denver.

The disease was imported to Northern Italy by a traveler from India who arrived June 21, 2007; got sick 2 days later; and somewhere along the line was bitten by the *A. albopictus* mosquitos endemic in that area of Italy. The virus quickly established itself in the regional *A. albopictus* population. The Italian outbreak ensued.

Could something similar occur in the United States? As it happens, *A. albopictus* is endemic throughout the Southeastern United States. The mosquito is thought to have arrived in 1985 via the port of Galveston, Tex., in a shipment of tires from Southeast Asia and has since gradually spread through much of the South. And 37 U.S. cases of Chikungunya fever imported from the Indian Ocean outbreak have been documented, including 5 viremic patients. Two of those five returned to Louisiana and South Carolina, states where *A. albopictus* is endemic. So perhaps a U.S. outbreak was a near miss.

Chikungunya fever is a dengue fever–like illness characterized by 2-5 days of sudden-onset high fever and chills, and a petechial or maculopapular rash, mainly on the trunk. This is followed by arthralgic disease that can last weeks or months. Indeed, the root of the word "Chikungunya" in Tanzania, where the virus was first isolated in the early 1950s, comes from a verb for "to become contorted" in local dialect, reflecting the severe joint symptoms.

Neurologic manifestations of Chikungunya fever in children include encephalitis, meningitis, and febrile seizures. In adults, meningitis and encephalitis can occur early, during the acute febrile stage of the disease, with acute neuropathy and myelitis occurring later.

Dr. Tyler offered Chikungunya fever as an example of an emerging CNS viral infection moving into new geographic regions as a result of expanded vector competence. But he noted that just as new viral diseases can emerge, once-familiar and important ones can recede or submerge, for unexplained reasons.

Case in point: Western equine encephalitis, which has mysteriously disappeared from the U.S. scene in recent years. There hasn't been a single reported case since the turn of the century. "The virus still circulates. It doesn't seem to be less virulent in mouse studies. It just doesn't seem to be an important cause of human encephalitis anymore. ... The virology does not seem to provide an explanation," he observed. "It makes one a little bit uncomfortable, because just like things can disappear they can reappear." ■