

# HPV Vaccine Exhibits Efficacy Beyond 6 Years

VITALS

**Major Finding:** At 6.4 years, vaccine efficacy against incident HPV infection was 95% in the according-to-protocol cohort.

**Source of Data:** A three-country, 27-site study of 1,113 women aged 15-26 years.

**Disclosures:** The study, led by Dr. Romanowski, was funded by GlaxoSmithKline (GSK) Biologicals, manufacturer of Cervarix. Dr. Clifford declared that he had no conflicts of interest.

BY MIRIAM E. TUCKER

The human papillomavirus 16/18 vaccine showed efficacy, sustained immunogenicity, and continued safety for up to 6.4 years in a combination of initial and follow-up placebo-controlled studies involving more than 1,000 women aged 15-26 years.

The human papillomavirus (HPV) vaccine, Cervarix, is now licensed in the United States, Europe, and elsewhere around the world. It contains the HPV types 16 and 18 adjuvanted with ASO4, comprising aluminum salt and an immunostimulatory molecule that has been shown to produce higher antibody titers that are sustained over a longer pe-

riod of time, compared with the same antigens adjuvanted with aluminum salts alone, according to the GSK Vaccine HPV-007 Study Group, led by Dr. Barbara Romanowski (Lancet 2009 Dec. 3 [doi:10.1016/S0140-6736(09)61567-1]).

Of 1,113 women included in the initial three-country, 27-site study, a total of 700 completed the follow-up study. The total vaccinated cohort included 560 women in the vaccine group and 553 in the placebo group, while the according-to-protocol (ATP) efficacy cohort included 465 in the vaccine group and 454 in the placebo group. At baseline, all had normal cervical cytology and were negative for both HPV-16 and -18.

The mean follow-up period from the start of the initial study was 5.9 years, with a maximum duration of 6.4 years. The study population was racially diverse, with a mean age of 20 years (range 15-26 years) at entry to the initial study and 23 years at the beginning

of the follow-up study.

At 6.4 years, vaccine efficacy against incident HPV-16 or HPV-18 infection in the ATP analysis was 95.3%, and long-term efficacy against persistent infection was 100% at both 6 and 12 months. In the total vaccinated cohort analysis, protection against cervical intraepithelial neoplasia grade 1 or higher associated with either vaccine HPV type was 100%. For the nonvaccine types HPV-31 and -45, vaccine efficacy against incident infection was 59.8% and 77.7%, while overall efficacy against any cervical intraepithelial neoplasia grade 2 or higher independent of HPV type was 71.9%, said Dr. Romanowski of the University of Alberta, Edmonton, and her associates.

Almost all vaccine recipients (99%) remained seropositive for anti-HPV-16 and anti-HPV-18 total IgG antibodies. After a peak response at 7 months, geometric mean titers for both antibodies reached a plateau between 18 and 24 months post vaccination, and remained stable thereafter. During months 63-76, antibody concentrations against HPV-16 and HPV-18 were at least 13-fold and 12-fold higher than were concentrations recorded fol-

lowing clearance of a natural infection in a previous study (Lancet 2007;369:2161-70).

Safety profiles of the HPV-16/18 vaccine and placebo were similar, with approximately one-third of each group reporting any adverse event, 10% or fewer reporting a serious adverse event, and less than 10% reporting new-onset chronic diseases. None of the serious adverse events was judged to be related to the vaccine, and there were no deaths.

In an accompanying editorial, Dr. Gary M. Clifford wrote that the data showing no evidence of further decline from 3 to 6 years are "perhaps the most interesting" because they suggest that mean antibody concentrations should remain well above those associated with natural infection long into the future.

The target age of vaccination is a balance between "being early enough to catch girls before sexual debut, but late enough to provide an as yet unknown duration of immunity that protects during as many subsequent years of sexual activity as possible," wrote Dr. Clifford of the International Agency for Research on Cancer, Lyon, France (Lancet 2009 Dec. 3 [doi:10.1016/S0140-6736(09)61789-X]). ■

## EXPERT OPINION

### Gardasil and Cervarix Are Not Interchangeable

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. 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.

Patients 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).



BY MICHAEL E. PICHICHERO, M.D.

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 currently 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.

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.

Although not specifically mentioned in Gardasil's label, 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 physicians 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 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 an-

other 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 never 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 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. ■

DR. PICHICHERO, a specialist in pediatric infectious diseases, is director of the Rochester (N.Y.) General Research Institute.