Assessing human papillomavirus vaccine efficacy and safety

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Human papillomavirus (HPV) is a common cause of genital warts, a common cause of genital infections, and it is also known to cause anogenital cancers. Patients with HPV infections are difficult to treat, from both a psychosocial and an economic perspective. Thus, the availability of a highly effective and safe vaccine to prevent HPV infection and its sequelae is very appealing.

Human papillomavirus types 6 and 11 are the most common strains that cause vulvovaginal warts, while HPV types 16 and 18 are implicated in most cases of vulvar, vaginal, cervical and anal cancers. In 2006, the United States Food and Drug Administration (FDA) approved a quadrivalent vaccine for protection against infection by these four strains. The vaccine is intended for use in girls and young women, aged 9 to 26 years, to prevent cervical intraepithelial neoplasia (CIN); cervical adenocarcinoma in situ (AIS); cervical cancer; vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VaIN) grades 2 and 3; and genital warts.

Efficacy and safety

The first proof-of-principle trial of this HPV vaccine, published in 2002, showed 100% efficacy in preventing persistent HPV type 16 infection in more than 1,000 female subjects aged 16 to 23 years.1 Subsequent HPV vaccine trials with both bivalent (HPV types 16, 18) and quadrivalent vaccines (HPV types 6, 11, 16, 18) have also demonstrated high efficacy in similar female populations.2-6 In all these trials, vaccine safety with no serious vaccine-related adverse events—together with a robust immune response—were demonstrated.

Additional safety and immunogenicity trials of the quadrivalent HPV vaccine in female and male subjects aged 10 to 15 years showed no serious vaccine-related adverse events—and higher geometric mean antibody titers—compared with female subjects aged 16 to 23 years.7

The federal Centers for Disease Control and Prevention’s (CDC’s) Advisory Committee on Immunization Practices (ACIP) recommends the routine administration of a quadrivalent vaccine for girls aged 11 and 12 years, with routine “catch-up” vaccination for girls and women aged 11 to 26 years.8 The quadrivalent HPV vaccine should be administered in three doses of 0.5 milliliter, with the second and third inoculations given two and six months after the first. The most commonly reported adverse events associated with this vaccine are pain, swelling, and erythema at the injection site.4,6
This three-dose schedule will effectively vaccinate most girls against HPV infection prior to the initiation of their sexual activity. However, women aged 19 to 26 years—the primary target group for slowing the spread of HPV infection—should be offered vaccination as part of their routine health maintenance. Vaccination should be offered to a woman even if she has already initiated sexual contact, because the quadrivalent vaccine has been shown to be effective in women who have been exposed to HPV.

It is important to keep in mind that the quadrivalent vaccine cannot be used as a treatment for patients with genital condyloma, neoplasia, or carcinoma.

From June 2006 (when the quadrivalent vaccine began to be used) through April 2008, the Vaccine Adverse Event Reporting System, of the CDC and FDA, received 15 reports of deaths following the quadrivalent vaccination in the United States. However, only 10 of these reports contained levels of information that were adequate for further analysis. After careful review of those reports, no causal relationship between vaccination and death could be established. For the remaining five reports of death, no patient-identifying information was available and, therefore, no confirmed death outcomes could be obtained.

The Vaccine Adverse Event Reporting System also received 31 reports of Guillain-Barré syndrome (GBS) in the United States from the time of the launch of the quadrivalent vaccine to the end of April 2008. Only 10 of these reports were confirmed cases of GBS after vaccination, and five of these cases involved simultaneous quadrivalent vaccination and use of meningococcal polysaccharide diphtheria toxoid conjugate. Of the remaining 21 reports, seven did not meet the case definition for GBS (when evaluated by the Clinical Immunization Safety Assessment network); one included symptoms of GBS prior to vaccination; four were unconfirmed cases of GBS; and nine required additional follow-up investigation.

**Insights from the FUTURE trials**

In the Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I and FUTURE II trials, 17,622 females, aged 16 to 23 years and 16 to 26 years, respectively, were enrolled. Enrolled subjects were not pregnant, had no history of abnormal cervical cytologic conditions, and reported no more than four sex partners during their lives. The subjects were randomized without regard to baseline HPV status to receive either the quadrivalent vaccine (HPV types 6, 11, 16, 18) or placebo (aluminum adjuvant only) on a schedule of 0, 2, and 6 months.

Per-protocol and intent-to-treat analyses were performed in the FUTURE trials. The per-protocol efficacy results were as follows: 100% efficacy against precancerous cervical lesions related to HPV types 16 and 18; 100% efficacy against high-grade VIN and VaIN related to HPV types 16 and 18; and 95% efficacy against CIN and AIS related to HPV types 6, 11, 16, and 18.

The intent-to-treat analysis in the FUTURE trials included subjects who had evidence of infection with one or more HPV vaccine types—either at study entry or before receiving the completed vaccine series.

This analysis included some subjects who did not complete the entire vaccine series. The intent-to-treat analysis showed the following efficacy results: 99% efficacy against CIN grades 2 and 3 and AIS related to HPV types 16 and 18; 94% efficacy against CIN grades 1 through 3 and AIS related to HPV types 6, 11, 16, and 18; and 90.9% efficacy against genital warts, VIN grades 1 through 3, and VaIN grades 1 through 3 related to HPV types 6, 11, 16, and 18. The quadrivalent vaccine was 100% effective (95% confidence interval [CI], 79%-100%) in preventing incident CIN grades 2 or 3 and cervical AIS caused by the HPV type(s) for which the women had tested negative at enrollment.

**Potential approval of bivalent vaccine on the horizon**

A bivalent vaccine against HPV types 16 and 18 is expected to receive FDA approval in 2009. Among 18,525 female subjects aged 15 to 25 years who were randomly assigned to receive one or more doses of either the bivalent HPV vaccine or a hepatitis A vaccine, an interim analysis found a 90.4% efficacy for prevention of CIN grades 2 and 3 among recipients of the HPV vaccine. In addition, the bivalent HPV vaccine showed 80% and 75.9% efficacy at 6 and 12 months, respectively, in preventing persistent HPV infection, and 89.2% efficacy in preventing CIN grade 1 among recipients.

In this bivalent vaccine trial, injections were given to subjects on a schedule of 0, 1, and 6 months. Pain at the injection site was—as with the quadrivalent vaccine—the most common bivalent-related adverse event observed.

**Follow-up findings**

In the quadrivalent vaccine trials, HPV type-specific competitive immunoassays with type-specific standards, measured in geometric mean titers, were used to assess subjects’ immunogenicity to each vaccine HPV type. These assays measured antibody levels against neutralizing epitope levels for each HPV type, using scales that are unique to each HPV type. The results of these assays showed that variations in dos-
virus-like particles (VLPs) were investigat-
ed by using pseudovirion infectivity assays
for HPV types 16, 31, 33, 35, 52, and 58—com pared with 48 such cases among
women in the placebo group (43% efficacy, 95% CI, 7-66, P < .05).15 The trial also
found a reduction with vaccination in persis-
te HPV infection caused by HPV types 31, 33, 35, 52, and 58 (109 cases
among vaccinees compared with 149 cases
among the placebo group: 28% efficacy, 95% CI, 7-44, P < .05).

Clinical trials have confirmed that cross-
protection may exist against nonvaccine
HPV types. After vaccination with a biva-
lent vaccine for HPV types 16 and 18,
broad protection beyond that anticipated
for those two HPV types—against incident
infection by HPV types 31 and 45—was
demonstrated in women.13

Additional long-term follow-up studies
are planned through the Association of the
Nordic Cancer Registries to assess duration
of HPV protection in patients after receipt
of quadrivalent vaccination.

Cross-protection against
nonvaccine HPV types
To obtain a better definition of cross-neu-
tralization among oncogenic HPVs, the
neutralizing activities of antibodies ob-
tained by immunization of mice with L1
virus-like particles (VLPs) were investigat-
ed by using pseudovirion infectivity assays
for HPV types 16, 31, 33, 45, 58, and 59.
In that study,14 the authors demonstrated
the existence of linear epitopes within the
L1 major capsid protein that induce cross-
neutralization against HPV type 16 and re-
lated HPV types.

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Additional evidence for cross-protection
was reported at the 47th Interscience Con-
ferece on Antimicrobial Agents and
Chemotherapy Meeting, held in Chicago
in September 2007. There, data was pre-
sented on a quadrivalent HPV vaccine trial
that included more than 9,000 women
who were randomized to receive either a
vaccine or placebo.15 The trial results
showed that, among women receiving the
quadrivalent vaccine, there were only 27
cases of precancerous lesions caused by
HPV types related to HPV type 16—that
is, HPV types 31, 33, 35, 52, and 58—compared with 48 such cases among
women in the placebo group (43% efficacy, 95% CI, 7-66, P < .05).15 The trial also
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Final notes
Vaccination against HPV infection should
be a routine part of every young woman’s
health maintenance. Osteopathic physi-
cians should incorporate the quadrivalent
HPV vaccine into their practices. The
ACIP recommends that girls be vaccinated
at age 11 or 12 years and that young
women aged 19 to 26 years also be vacci-
nated—regardless of whether they have ini-
tiated sexual activity. Physicians must make
it clear to their patients that the quadriva-
lent HPV vaccine is for prophylactic pur-
puses; it is not a treatment for women with
genital condyloma, neoplasia, or carcino-
ma.

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