The bivalent vaccine is approved in the United States for prevention of cervical cancer, CIN ≥2, adenocarcinoma in situ, and CIN 1 caused by HPV-16 and -18. This vaccine is approved for administration to girls and women 9–25 years of age.

Quadrivalent Vaccine (Gardasil) A quadrivalent L1 VLP (HPV-6, -11, -16, and -18) vaccine, marketed under the name Gardasil (Merck), is administered IM at months 0, 2, and 6. A combined efficacy analysis based on data from four randomized double-blind clinical studies including more than 20,000 participants demonstrated that the vaccine's efficacy against external genital warts was 98.9% (95% CI, 93.7 to 100). Its efficacy was 95.2% (95% CI, 87.2 to 98.7) in protecting against CIN, 100% (95% CI, 92.9 to 100) against HPV-16- or HPV-18-related CIN 2/3 or adenocarcinoma in situ, and 100% (95% CI, 55.5 to 100.0) against HPV-16- or HPV-18-related vulvar intraepithelial neoplasia grades 2 and 3 (VIN 2/3) and vaginal intraepithelial neoplasia grades 2 and 3 (VaIN 2/3).

Safety data on the quadrivalent HPV vaccine are available from seven clinical trials including nearly 12,000 girls and women 9–26 years of age who received the vaccine and ~10,000 who received placebo. A larger proportion of young women reported injection-site adverse events in the vaccine groups than in the aluminum-containing or saline placebo groups. Systemic adverse events were reported by similar proportions of vaccine and placebo recipients and were described as mild or moderate by most participants. The types of serious adverse events reported were similar for the two groups. Ten persons who received the quadrivalent vaccine and seven persons who received placebo died during the course of the trials; no deaths were considered to be vaccine related.

During the course of the quadrivalent vaccine trials, surveillance data on the development of new medical conditions were collected for up to 4 years after vaccination. No statistically significant differences in the incidence of any medical conditions between vaccine and placebo recipients were found; this result indicated a very good safety profile. A recent safety review by the U.S. Food and Drug Administration and the Centers for Disease Control and Prevention (CDC) examined events related to Gardasil that had been reported to the Vaccine Adverse Events Reporting System. Adverse events were consistent with those seen in previous safety studies of the vaccine. It is noteworthy that rates of syncope and venous thrombotic events were higher with Gardasil than those that have usually been documented for other vaccines.

The quadrivalent vaccine is approved for (1) vaccination of girls and women 9–26 years of age to prevent genital warts and cervical cancer caused by HPV-6, -11, -16, and -18; (2) vaccination of the same population to prevent precancerous or dysplastic lesions, including cervical adenocarcinoma in situ, CIN 2/3, VIN 2/3, VaIN 2/3, and CIN 1; (3) vaccination of boys and men 9–26 years of age to prevent genital warts caused by HPV-6 and -11; and (4) vaccination of individuals 9–26 years of age to prevent anal cancer and associated precancerous lesions due to HPV-6, -11, -16, and -18.

Cross-Protection of HPV Vaccines Women vaccinated with either of the available vaccines produce neutralizing antibodies against types related to HPV-16 or -18. Analyses of data from clinical trials suggest that both vaccines may offer cross-protection against nonvaccine types. The bivalent vaccine appears more efficacious against HPV-31, -33, and -45 than the quadrivalent vaccine, but differences in study design make direct comparisons difficult. In addition, vaccine efficacy against persistent infections with HPV-31 and -45 appeared to wane over time in the bivalent vaccine trials, whereas efficacy against persistent infection with HPV-16 or -18 remained stable.

Second-Generation Vaccines While HPV-16 and -18 cause the majority of cervical cancers worldwide, global data have shown that HPV-31, -33, -35, -45, -52, and -58 are the next most frequently detected types in invasive cervical cancers. Second-generation vaccines that are in development incorporate VLPs of additional oncogenic HPV types (other than HPV-16 and -18), including HPV-31, -33, -45, -52, and -58; efficacy studies are ongoing. If vaccines with these five additional oncogenic types prove to be effective, mathematical models estimate that the level of protection could be raised to 90% of all squamous cell cervical cancers worldwide.

Recommendations for Vaccination The CDC's Advisory Committee for Immunization Practice recommends administration of the quadrivalent HPV vaccine—with the schedule used in the vaccine trials—to all boys and girls 11–12 years of age as well as to boys/men and girls/women 13–26 years of age who have not previously been vaccinated or who have not completed the full series. For women, Papanicolaou (Pap) smear testing and screening for HPV DNA are not recommended before vaccination. After vaccination, Pap testing is recommended to detect disease caused by other oncogenic HPV types.

PREVENTION OF HPV-ASSOCIATED DISEASE

After HPV infection occurs, prevention of HPV-associated disease relies on screening. Women residing in developing countries who lack access to cervical screening programs have a higher rate of cervical cancer and a lower rate of cancer-specific survival. Approximately 75% of women living in developed countries have been screened in the past 5 years, whereas the figure is only ~5% among women living in developing countries. Economic and logistic obstacles likely impede routine screening of these populations for cervical cancer.

The primary method used for cancer screening is cervical cytology via Pap smear. The guidelines of the American Society of Colposcopy and Cervical Pathology recommend initiation of cervical cancer screening at age 21, regardless of the age of sexual debut. Women 21–29 years old with a normal Pap smear should have the test repeated every 3 years. Although adolescent and young women often test positive for HPV DNA, they are at very low risk of cervical cancer. Co-testing, or testing for HPV DNA at the time of the Pap smear, is not recommended for women in this age group because the presence of HPV DNA does not correlate with the presence of high-grade squamous intraepithelial neoplasia. Women 30–65 years of age should have a Pap smear every 3 years if testing for HPV DNA is not performed. The screening interval for women in this age group can be extended to every 5 years if co-testing results are negative. HPV testing is not recommended for partners of women with HPV or for screening for conditions other than cervical cancer.

Currently, there is no clear consensus regarding screening for anal cancer and its precursors, including high-grade anal intraepithelial lesions. This lack of clarity is due to an inadequate understanding of optimal treatment for low- or high-grade anal dysplasia found during cytologic screening. The current HIV treatment guidelines suggest that there may be a benefit to screening, but an effect on the associated morbidity and mortality of anal squamous cell cancer has not been consistently demonstrated.

TREATMENT HPV-ASSOCIATED LESIONS

OVERVIEW AND GENERAL RECOMMENDATIONS

A variety of treatment modalities are available for various HPV infections, but none has been proven to eliminate HPV from tissue adjacent to the destroyed and infected tissue. Treatment efficacies are limited by frequent recurrences (presumably due to reinfection acquired from an infected partner), reactivation of latent virus, or autoinoculation from nearby infected cells. The goals of treatment include prevention of virus transmission, eradication of premalignant lesions, and reduction of symptoms.

Treatment is generally successful in eliminating visible lesions and grossly diseased tissue. Different therapies are indicated for genital warts, vaginal and cervical disease, and perianal and anal disease.

An optimal therapy for HPV-related genital tract disease that combines high efficacy, low toxicity, low cost, and low recurrence rate is not available. For genital warts of the penis or vulva, cryotherapy (see below) is safest, least expensive, and most effective. Guidelines for the treatment of genital warts can be found on the CDC website (*www.cdc.gov/std/treatment/2010/genital-warts.htm*). Women with vaginal