Quadrivalent Human Papillomavirus Vaccine

Eliav Barr and Gretchen Tamms
Merck Research Laboratories, West Point, Pennsylvania

The lifetime risk of human papillomavirus (HPV) infection exceeds 50%. HPV infection causes >550,000 cases of cervical and anogenital cancer worldwide annually. Infection also causes precancerous lesions and genital warts. HPV types 16 and 18 cause ~70% of HPV-related cancers, and HPV types 6 and 11 cause ~90% of cases of genital warts. A quadrivalent vaccine for HPV types 6, 11, 16, and 18 (HPV 6/11/16/18) has been developed for prevention of cervical cancer, genital warts, and vulvar and vaginal precancerous lesions. Prophylactic vaccination of young women was 96%–100% effective in preventing HPV 6/11/16/18–related cervical and anogenital precancers and genital warts. Efficacy remained high for at least 5 years following vaccination. Postvaccination anti-HPV levels in adolescents were superior to those observed in women (the population in which efficacy was shown). Vaccination was generally well tolerated. The vaccine is licensed in 180 countries. It has been added to national vaccination programs, including that of the United States. Widespread use of HPV 6/11/16/18 vaccine is expected to greatly reduce the incidence of HPV-related cancers, precancers, and genital warts.

Clinical Burden of Human Papillomavirus (HPV) Infection

The lifetime risk of HPV infection is >50% [1]. HPV infection can cause cancer (most commonly in the cervix), genital warts, and recurrent respiratory papillomatosis (RRP) [2–9].

Every year, >490,000 women receive a diagnosis of cervical cancer, and ~290,000 die from the disease [10]. In developed countries, Papanicolou (Pap) testing has largely shifted the burden of HPV disease from managing cervical cancer to managing the care of millions of women with dysplastic lesions (cervical intraepithelial neoplasia [CIN] grades 1, 2, and 3 or low-, moderate-, and high-grade dysplasia, respectively) [11]. Despite the availability of screening, ~12,000 American women receive a diagnosis of cervical cancer annually [12]. Cervical adenocarcinoma is poorly detected by screening; the incidences of this cancer and its precursor, adenocarcinoma in situ (AIS), are increasing [13–15]. In developing countries, the lack of screening programs has resulted in a high incidence of cervical cancer [10].

HPV infection also causes 83%–95% of cases of anal cancer, 20%–50% of cases of vulvar cancer, 60%–65% of cases of vaginal cancer, and 30%–42% of cases of penile cancer [16]. Approximately 6300 Americans will die from such cancers (including both HPV-related and non–HPV-related cases) annually [17]. Like cervical cancer, these cancers are preceded by dysplasia (e.g., vulvar intraepithelial neoplasia and vaginal intraepithelial neoplasia).

The lifetime risk for acquisition of genital warts is >10% [18]. Men and women who develop genital warts have a high incidence of depression, sexual dysfunction, and disruptions to long-term relationships [19]. Ablation is successful in clearing 70% of cases, but recurrence is common [20]. Approximately 6000 Americans receive a diagnosis of RRP annually. RRP is caused by laryngeal HPV infection. The disease causes airway obstruction, requiring frequent laser excision to remove the tumors and often leading to tracheostomy and loss of the ability to speak. Spread to the distal airways and malignant transformation are often fatal [7–9].

HPV Virology

HPV is a nonenveloped capsid virus containing double-stranded DNA [21]. The viral genome contains early (E) genes and late (L) genes. The E6 and E7 proteins are oncogenic and disrupt cell cycle control proteins, thereby inducing excessive and disordered cell proliferation. L genes encode for viral capsid proteins. Approximately 40 HPV types infect the genital tract. These types are divided into high-risk (i.e., cancer-causing) types (e.g., HPV 16) and low-risk types that cause generally benign tumors (e.g., HPV 6) [21].
Table 1. Clinical program for quadrivalent human papillomavirus (HPV) types 6, 11, 16, and 18 (HPV 6/11/16/18) vaccine.

<table>
<thead>
<tr>
<th>Objective, study</th>
<th>Study type</th>
<th>No. of subjects</th>
<th>Study population</th>
<th>End point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>005 [41], 007 [42], 013 (Future I) [31], 015 (Future II) [32]</td>
<td>Phase II and III</td>
<td>20,877</td>
<td>Women aged 16–26 years</td>
<td>HPV 16/18–related CIN 2/3 and AIS; HPV 16/18–related VIN 2/3 and VaIN 2/3; HPV 6/11/16/18–related CIN or AIS; HPV 6/11/16/18–related external genital warts</td>
</tr>
<tr>
<td>019</td>
<td>Phase III</td>
<td>3800</td>
<td>Women aged 24–45 years</td>
<td>HPV 6/11/16/18–related infection or disease</td>
</tr>
<tr>
<td>020</td>
<td>Phase III</td>
<td>3900</td>
<td>Men aged 16–26 years</td>
<td>HPV 6/11/16/18–related infection; HPV 6/11–related genital warts; HPV 6/11/16/18–related anal precancer</td>
</tr>
</tbody>
</table>

| Immunogenicity  |            |                 |                  |           |
| Immunogenicity  |            |                 |                  |           |
| 007             | Phase II   | 241              | Women aged 16–23 years | Anti-HPV levels through 5 years [44]; demonstration of immune memory [45] |
| 013             | Persistence| 5455             | Women aged 16–26 years | Anti-HPV levels through 4 years |
| 015             | Persistence| 12,167           | Women aged 16–26 years | Anti-HPV levels through 4 years |
| 016 [49]        | Adolescent-I | 1529           | Women aged 16–23 years, adolescents aged 9–15 years | Bridge efficacy findings from young women to adolescent boys and girls |
| 018 [46]        | Adolescent-2 | 1781           | Adolescents aged 9–15 years | Anti-HPV levels through 6 years in adolescent boys and girls |

| Safety          |            |                 |                  |           |
| Safety          |            |                 |                  |           |
| All             | All        | 21,464           | Women aged 16–26 years; adolescents aged 9–15 years | Local and systemic adverse experiences; long-term medical history; pregnancy and breastfeeding outcomes |

NOTE. AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia; VaIN, vaginal intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia.

QUADRIVALENT HPV RECOMBINANT MAJOR CAPSID (L1) VIRUS-LIKE PARTICLE (VLP) VACCINE

Studies to select HPV vaccine candidates were conducted in preclinical models of papillomavirus disease [22]. Immunization with VLPs of the L1 protein of these papillomaviruses induced serum anti-L1 neutralizing antibodies and resulted in protection from infection. Unvaccinated animals that received serum transfusions from vaccinated animals were also protected from infection. These results suggested that induction of systemic anti-HPV responses by HPV L1 VLP vaccines would result in protection against type-specific HPV infection and disease.

The quadrivalent HPV vaccine bears the trade name Gardasil (Merck) and contains VLPs of the L1 protein of HPV types 6, 11, 16, and 18 (HPV 6/11/16/18) synthesized in Saccharomyces cerevisiae and adsorbed on amorphous aluminum hydroxyphosphate sulfate adjuvant. HPV types 16 and 18 cause 70% of cervical cancers [23], 50%–60% of CIN 2 and 3 lesions [24], and ~25% of CIN 1 lesions [25]. Of the remaining high-risk HPV types, none is responsible for >5% of cervical cancers. HPV types 6 and 11 cause 90% of genital wart and RRP lesions and 5% of CIN 1 lesions [26–28]. Because the vaccine does not contain live virions, it is incapable of causing infection. The vaccine is administered by intramuscular injection in a regimen consisting of an initial dose, a dose administered 2 months later, and a dose administered 6 months later.

EFFICACY STANDARDS FOR LICENSURE OF HPV VACCINES

Ideally, licensure of an HPV vaccine should be predicated on a demonstration of the efficacy of the vaccine against cervical cancer caused by vaccine HPV types. Phase III trials using a cervical cancer end point are not feasible, because the time from acquisition of infection to the development of cancer often exceeds 20 years, and the standard of care is to screen for and excise CIN 2 and 3 or AIS lesions prior to invasion. Instead, trials to evaluate the impact of HPV vaccines on cervical cancer risk must use surrogate markers.

High-risk HPV infection is the first, necessary step in the development of cervical cancer. CIN 1 is a manifestation of early HPV infection and is not necessarily a precursor to cervical cancer. Both infection and CIN 1 tend to resolve spontaneously. In contrast, CIN 3 and AIS are the immediate and obligate precursors of squamous cell and adeno carcinoma of the cervix, respectively. CIN 2 is also considered to be high-grade dysplasia, although a histologic diagnosis of CIN 2 is less reproducible than one of CIN 3, and spontaneous regression is more common for CIN 2 than for CIN 3 [29]. Pap testing reduces cervical cancer rates by facilitating detection (and ex-
Table 2. Baseline (vaccination day 1) characteristics of women aged 16–26 years enrolled in the efficacy program for quadrivalent human papillomavirus (HPV) types 6, 11, 16, and 18 vaccine.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subjects (n = 20,887)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years</td>
<td>20</td>
</tr>
<tr>
<td>Sexually active</td>
<td>94</td>
</tr>
<tr>
<td>Age at sexual debut, mean years</td>
<td>17</td>
</tr>
<tr>
<td>Mean lifetime number of sexual partners</td>
<td>2</td>
</tr>
<tr>
<td>Prior pregnancy</td>
<td>22</td>
</tr>
<tr>
<td>Using hormonal contraceptive</td>
<td>58</td>
</tr>
<tr>
<td>Test result positive for chlamydia</td>
<td>4</td>
</tr>
<tr>
<td>Papanicolou test diagnosis of ASC-US or greater</td>
<td>12</td>
</tr>
<tr>
<td>PCR or serological test result positive for HPV type 6, 11, 16, or 18</td>
<td>27</td>
</tr>
</tbody>
</table>

NOTE. Data are percentage of subjects, unless otherwise indicated. ASC-US, atypical squamous cells of undetermined significance.

detection) of these lesions prior to invasion. Thus, the US Food and Drug Administration and the World Health Organization [30] have stated that licensure of HPV vaccines requires a demonstration that vaccination reduces the incidence of CIN 2 and 3 or AIS caused by vaccine HPV types.

DESIGN OF THE QUADRIVALENT HPV VACCINE CLINICAL PROGRAM

Efficacy studies. The efficacy studies (table 1) used a range of end points. Early studies that evaluated efficacy with regard to HPV infection rates were used as proofs-of-concept. Studies with end points that included CIN (of any grade) and genital warts (e.g., protocol 013 [Future I] [31]) evaluated the impact of the vaccine on the burden of cervical and genital HPV disease. Studies with end points limited to CIN 2 and 3 or AIS (e.g., protocol 015 [Future II] [32]) evaluated the impact of the vaccine on cervical cancer rates. Prespecified analyses of the combined phase II and III database were used to improve the precision of the efficacy observed in individual trials [33] and to evaluate efficacy with regard to vulvar intraepithelial neoplasia 2 and 3 and vaginal intraepithelial neoplasia 2 and 3 [34].

Study populations. HPV infection is sexually transmitted. Most women experience sexual debut when they are 16–25 years of age [35, 36]. By 5 years after sexual debut, up to 50% of women will have been infected with at least one HPV type [37–39]. Accordingly, efficacy trials were conducted in women aged 16–26 years. The studies did not have screening phases; women were enrolled regardless of their HPV status or Pap test result on day 1. Thus, the vaccine was tested in the manner in which its postlicensure use was envisioned (i.e., without prescreening). Although these clinical trials included a broad representation of women from developed and developing countries, 16–26-year-old women with >4 or >5 lifetime sex partners and women with a past history of abnormal Pap test results or genital warts were not enrolled.

HPV vaccination programs will include sexually naive adolescents. Studies involving adolescents were limited to immunogenicity and safety evaluations (collection of genital samples was not feasible).

Efficacy studies were initially conducted in women, because the burden of HPV infection falls disproportionately on women. Efficacy studies involving men are ongoing (table 1).

Disease ascertainment. Liquid-based cytology specimens were collected at 6–12-month intervals and read at a central laboratory (Diagnostic Cytology Laboratories, Indianapolis, IN). Subjects were referred to colposcopy according to protocol-mandated algorithms that mirrored international standards of care. During colposcopy, each abnormal area was biopsied. Referral to definitive therapy was protocol-mandated.

Detection of genital wart lesions included routine genital inspection visits and unscheduled visits for symptoms. Lesions

Table 3. Primary efficacy results with combined database of efficacy studies of human papillomavirus (HPV) types 6, 11, 16, and 18 (HPV 6/11/16/18) vaccine (per-protocol population).

<table>
<thead>
<tr>
<th>End point</th>
<th>HPV vaccine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of subjects</td>
<td>No. of cases</td>
</tr>
<tr>
<td>HPV 16– or HPV 18–related CIN 2 or 3 or AIS</td>
<td>8492</td>
<td>1b</td>
</tr>
<tr>
<td>HPV 16– or HPV 18–related VIN 2 or 3</td>
<td>7771</td>
<td>0</td>
</tr>
<tr>
<td>HPV 16– or HPV 18–related VaIN 2 or 3</td>
<td>7771</td>
<td>0</td>
</tr>
<tr>
<td>HPV 6–, HPV 11–, HPV 16–, or HPV 18–related CIN (CIN 1, CIN 2/3) or AIS</td>
<td>7863</td>
<td>6</td>
</tr>
<tr>
<td>HPV 6–, HPV 11–, HPV 16–, or HPV 18–related genital warts</td>
<td>7899</td>
<td>2</td>
</tr>
</tbody>
</table>

NOTE. Point estimates and 95% CIs are adjusted for person-time of follow-up. Median duration of follow-up is 3 years after vaccination dose 1. AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia; VaIN, vaginal intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia.

a With at least 1 follow-up visit after month 7.
b The single case of HPV 16–positive CIN grade 3 in the vaccine group occurred in a patient who was positive for HPV type 52 at baseline, as well as in 5 histologic specimens collected at the time of diagnosis and treatment. HPV 16 DNA was detected in 1 histologic specimen but at no other time point.
suspected to be HPV-related and lesions whose clinical diagnosis was unknown were biopsied.

All tissue specimens were processed and read at the central laboratory. Biopsy and definitive therapy specimens were reviewed by a pathology panel that was blinded to all HPV test results and to vaccination status. The panel’s consensus diagnoses were used in the assignment of study end points. All tissue specimens were tested to identify the causal HPV type in the lesion.

**Immunogenicity.** Competitive luminex immunoassays that detect serum anti-HPV responses that compete against monoclonal antibodies for binding to epitopes critical for virus entry (i.e., antibodies with neutralizing potential) have been developed [40]. Using these assays, studies evaluated the immune responses at the completion of the vaccination regimen and for up to 4.5 years thereafter. These studies were also designed to bridge efficacy findings from sexually active women in whom efficacy was evaluated to sexually naive adolescents in whom efficacy studies were not feasible.

**Safety.** Subjects were evaluated for injection site and systemic tolerability, impact on long-term health status, and interaction with pregnancy.

**Statistics.** The quadrivalent HPV vaccine is a prophylactic vaccine; it prevents incident infections, but it does not impact infections already present at vaccination onset [31, 32]. Because the studies did not have a screening phase and women were enrolled regardless of their day 1 HPV status or Pap test result, we conducted the primary efficacy analyses in the subset of subjects who were not infected with HPV 6, 11, 16 or 18 before vaccination. The primary efficacy analyses were conducted in HPV type 6, 11, 16, and/or 18–specific per-protocol susceptible populations, which consisted of subjects who were DNA negative and seronegative for the relevant HPV type(s) at enrollment, remained DNA negative for the same HPV type(s) through 1 month after dose 3, received all 3 doses of vaccine or placebo within 1 year, and did not violate the protocol. Case ascertainment started 1 month after administration of the third dose [31, 32].

Supportive analyses were conducted in an unrestricted susceptible population. This population included all subjects who were naive to the relevant HPV type at enrollment and had received at least 1 injection. Vaccine efficacy was also estimated in an intention-to-treat general population that included all randomized subjects, regardless of baseline HPV status. In the present article, case ascertainment in these populations started 30 days after dose 1.

Type-specific per-protocol immunogenicity cohorts were defined as members of the per-protocol population who were vaccinated and had serum samples collected during predefined time frames.
EFFICACY, IMMUNOGENICITY, AND SAFETY RESULTS

Efficacy was assessed in 4 randomized, double-blind, placebo-controlled studies that together randomized 20,887 women aged 16–26 years [31, 32, 41, 42]. Table 2 describes the demographic characteristics of these subjects. Overall, 27% of subjects were positive for at least 1 vaccine HPV type by serological testing and/or PCR. However, among positive subjects, 74% were positive to only 1 vaccine HPV type and were at risk for infection due to the remaining vaccine HPV types.

Table 3 summarizes the primary efficacy analysis in young women. Prophylactic administration of a 3-dose regimen of quadrivalent HPV vaccine was highly effective in preventing HPV type 16– and type 18–related CIN 2 and 3, AIS, vulvar intraepithelial neoplasia types 2 and 3, and vaginal intraepithelial neoplasia types 2 and 3 (and by inference, HPV type 16– and type 18–related cervical, vulvar, and vaginal cancer); HPV 6/11/16/18-related CIN or AIS; and HPV 6/11/16/18–related genital warts. Among subjects who were already infected with ≥1 vaccine HPV type at enrollment, vaccination was efficacious in preventing disease caused by the remaining vaccine HPV types [43].

The general population of young women includes those who are naïve to vaccine HPV types and those who are infected with ≥1 vaccine HPV type. The impact of the quadrivalent HPV vaccine in the general clinical trial population (all randomized woman who had follow-up, including those with prevalent anogenital disease, HPV 6/11/16/18 infection, and/or infection with other high-risk or low-risk HPV types before vaccination) is shown in table 4 and figure 1. This analysis population approximates efficacy in the general population of women, most of whom are already sexually active and who may be infected with ≥1 HPV type before vaccination. Prophylactic efficacy in the unrestricted susceptible population, which denotes the vaccine’s efficacy among enrolled subjects who were naïve to the relevant HPV types at vaccination onset, is provided for comparison. The unrestricted susceptible analysis population approximates the general population of sexually naïve adolescents and women with few lifetime sex partners. Because the quadrivalent HPV vaccine is prophylactic, it does not impact the course of infection present before vaccination onset. Accordingly, in the general clinical trial population, vir-
Table 5. Human papillomavirus (HPV) vaccine–related injection site and systemic adverse events.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Percentage of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HPV vaccine group (n = 5088)</td>
</tr>
<tr>
<td>Injection site (occurring 1–5 days after vaccination)</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>83.9</td>
</tr>
<tr>
<td>Swelling</td>
<td>25.4</td>
</tr>
<tr>
<td>Erythema</td>
<td>24.6</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3.1</td>
</tr>
<tr>
<td>Systemica (occurring 1–15 days after vaccination)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>10.3</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.2</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.8</td>
</tr>
</tbody>
</table>

**NOTE.** The vaccine-related adverse events that were observed among recipients of quadrivalent HPV vaccine were at a frequency of at least 1.0% and also at a greater frequency than that observed among placebo recipients.

a The most frequently reported serious systemic adverse events among quadrivalent HPV vaccine recipients, regardless of causality, were headache (0.03% of vaccine recipients vs. 0.02% of placebo recipients), gastroenteritis (0.03% vs. 0.01%), appendicitis (0.03% vs. 0.01%), pelvic inflammatory disease (0.02% vs. 0.02%), and urinary tract infection (0.02% vs. 0.02%).

The vaccine’s efficacy and immunogenicity were evaluated through 5 years after dose 1 in the phase Ib study V501-007 [44, 45]. In the per-protocol population, efficacy with respect to the incidence of persistent HPV 6/11/16/18 infection or related disease was 95.8% (95% CI, 83.8–99.5). No cases of breakthrough infection caused by waning immunity were observed. That is, no cases were observed among vaccine recipients during the persistence phase (months 36–60) [44]. Figure 2 displays serum anti-HPV geometric mean titers (GMTs) measured in the study. The highest measured anti-HPV GMTs were at month 7. GMTs decreased thereafter but then reached a plateau that remained stable through year 5. Administration of a challenge dose of vaccine at year 5 to the group that received vaccine at study onset resulted in strong anamnestic responses, demonstrating the induction of long-lived immune memory [45]. A comparison of the vaccine-induced anti-HPV GMTs with those associated with natural infection can be found in Olson et al. [45].

Figure 2 also displays anti-HPV GMTs among adolescents at months 7 and 18. At both time points, vaccination of adolescents induced higher anti-HPV GMTs, compared with vaccination of adults. Month 18 anti-HPV responses for HPV types 6, 11, 16, and 18 in girls aged 9–15 years were 213, 300, 1250, and 181 mMU/mL [46], respectively; in women, they were 102, 106, 558, and 80 mMU/mL, respectively.

Vaccination was generally well tolerated. The proportions of subjects with serious adverse experiences were comparable between the vaccine and placebo groups. Few subjects discontinued vaccination because of an adverse event. Table 5 displays the proportion of subjects in the vaccine, adjuvant-containing placebo, and saline placebo groups who reported an injection site adverse event. Compared with the saline placebo group, administration of the vaccine and adjuvant-containing placebo was associated with higher incidences of injection site adverse events. Subjects who received vaccine were more likely to report fever than were subjects in the placebo group. Temperatures >39°C were rare. A total of 206 of 21,464 subjects who received quadrivalent vaccine or placebo reported a serious systemic adverse event (table 5). During all of the clinical studies combined, 18 deaths were reported (11 in subjects who received vaccine and 7 in subjects who received placebo). None of the deaths were judged to be vaccine or placebo related. The most common causes of death were motor vehicle accidents (7 subjects) and overdose and/or suicide (4 subjects).

During the studies, 2832 women (1396 of whom received vaccine, and 1436 of whom received placebo) reported at least 1 pregnancy. Overall, the proportions of pregnancies with an adverse outcome were comparable between groups. Congenital anomalies were detected in 25 and 22 pregnancies that occurred...
in vaccine and placebo subjects, respectively. For pregnancies with estimated onset within 30 days of vaccination, 5 and 0 cases of congenital anomaly were observed in the vaccine and placebo groups, respectively. The congenital anomalies observed in these 5 infants were relatively common and pathogenetically unrelated, suggesting different etiologies. In pregnancies with onset >30 days after vaccination, 20 and 22 cases of congenital anomaly were observed in the vaccine and placebo groups, respectively. Review by an external specialist blinded to treatment group concluded that the types of anomalies observed were diverse and consistent with those generally observed in pregnancies in women aged 16–26 years.

**COST EFFECTIVENESS**

In early follow-up (within the first 2 years) of the intention-to-treat population (the general population of women, regardless of baseline HPV status) of the phase III study V501-013, administration of quadrivalent HPV vaccine reduced the incidence of definitive therapy (e.g., loop electrosurgical excision procedure) by 16.5% (95% CI, 2.9%–28.2%) and the incidence of genital wart excision procedures by 26.5% (95% CI, 3.6%–44.2%), compared with placebo. This reduction underestimates the long-term cost-effectiveness of the vaccine, because most procedures that occurred early in the studies were the result of disease caused by infection already present at day 1. When analyses were limited to subjects who were followed up for at least 2.5 years, the benefit of the vaccine became even more apparent, because percentage reductions in overall HPV disease–related health care costs for the vaccine arm, compared with the placebo arm, nearly tripled between years 1 and 3 of follow-up (data not shown).

Separately, economic analyses using population-dynamic models of HPV infection, transmission, and disease for the United States have demonstrated that universal vaccination of girls and women aged 12–24 years is cost-effective, compared with other currently accepted US health care practices, costing $4666 per quality-adjusted life-year [47]. This strategy was shown to yield substantially larger and more rapid health benefits than vaccinating only girls aged 12 years without catch-up vaccination, and it was shown to be cost-effective ($10,362 per quality-adjusted life-year), compared with a more limited female catch-up vaccination strategy for girls and women aged 12–19 years [47] (data not shown).

**PUBLIC HEALTH IMPLEMENTATION**

The quadrivalent vaccine has the potential to greatly reduce the incidence of both forms of life-threatening HPV disease (cancer and RRP) and strengthen the rationale for vaccination of both sexes (prevention of genital warts and RRP), which will result in high vaccine coverage and herd immunity. The quadrivalent HPV vaccine has been licensed in >80 countries. In the United States, the vaccine is licensed for use in females aged 9–26 years. The US Advisory Committee for Immunization Practices and the American Academy of Pediatrics have recommended routine vaccination of girls aged 11–12 years and routine catch-up vaccination for girls and women aged 13–26 years. The vaccine is included in the Vaccines for Children program. Implementation programs have been announced in Australia, Canada, and Europe. Efforts to rapidly introduce the vaccine into developing countries are underway.

**REMAINING QUESTIONS**

**Cross-protection.** HPV types 16 and 18 are prototypes for 2 sets of serologically related cancer-causing HPV types. Although HPV types 16 and 18 cause 70% of cases of cervical cancer in the United States, these related types (i.e., 31 and 45) cause most of the remaining HPV-related cancers. Owing to cross-reactivity, HPV vaccines targeting HPV types 16 and 18 may also reduce the incidence of infection due to these related HPV types [48]. Definitive evaluations are underway.

**Replacement.** Although studies have suggested that the course of an HPV infection is not impacted by concurrent infection with another type [24], it remains possible that eradication of common HPV types may cause an upsurge in infection with nonvaccine HPV types. Studies to monitor for this phenomenon are being instituted.

**Duration of efficacy.** Vaccine efficacy remains high for at least 5 years [44]. Longer-term follow-up in adolescents and adults is underway.

**Efficacy in women aged >26 years.** Sexually active women of all ages remain at risk for HPV infection. Women who clear infection with a vaccine HPV type may not enjoy lifelong protection from recurrence of that infection. An efficacy study involving women aged 24–45 years is underway.

**Efficacy in men.** All sexually active men are at risk for genital warts. Men who have sex with men are at risk for anal cancer. Men transmit HPV infection to women. Because this vaccine was highly effective in preventing HPV-related lesions arising in the more-keratinized epithelium of the external genitalia of women, it is likely that the quadrivalent HPV vaccine will be as efficacious in men as it is in women; however, efficacy in men has not been proven, and an efficacy study is ongoing.

**Impact on other HPV-related diseases.** The quadrivalent HPV vaccine should reduce the incidence of RRP and penile cancer and could potentially reduce the incidence of head and neck cancer. Long-term studies to evaluate the impact of the vaccine on the incidence of these diseases are planned.

**Broader coverage.** The potential cross-protective efficacy of first generation HPV vaccines notwithstanding, a vaccine that targets a broader range of HPV types will further reduce
the overall burden of HPV-related cancer. Studies of a broad-spectrum second-generation HPV vaccine are underway.

**SUMMARY**

HPV-related cancers and other lesions represent a substantial public health burden. Prophylactic administration of a quadrivalent HPV 6/11/16/18 vaccine to young women is highly effective in reducing their risk of HPV type 16– and type 18–related cervical, vulvar, and vaginal cancers and HPV 6/11/16/18–related cervical dysplasia and genital warts. Implementation programs are underway. Further studies to evaluate the vaccine’s duration of efficacy, its capacity to impact disease caused by nonvaccine HPV types, and its efficacy in men and older sexually active women are ongoing. Immunization with this vaccine holds promise for reducing the overall burden of clinical HPV disease, including HPV-related cancers.

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**References**