

# Harnessing the power of prevention: human papillomavirus vaccines

Edward J. Mayeaux, Jr.

Human papillomavirus (HPV) infection and HPV-associated diseases pose a considerable health care burden in the United States. The morbidity and mortality associated with HPV infection and HPV-associated diseases, ranging from genital warts to cervical cancer, have prompted both the use of screening measures to monitor HPV infection and the development of numerous treatment modalities to address its clinical sequelae. Although screening programs have dramatically reduced the incidence of cervical cancer through early detection and treatment, this devastating illness, which frequently affects women of reproductive age, remains a major public health concern. Prophylactic vaccines that prevent HPV infection have proved to be safe, well tolerated, highly efficacious, and induce long-lasting immunity to HPV. Multivalent vaccines that protect against the most common disease-causing HPV types should significantly reduce the morbidity and mortality associated with HPV.

## Keywords

cervical cancer, genital warts, human papillomavirus (HPV), vaccine

Curr Opin Obstet Gynecol 18 (suppl 1):S15–S21. © 2006 Lippincott Williams & Wilkins.

Department of Obstetrics and Gynecology, Louisiana State University Health Sciences Center, Shreveport, Louisiana, USA

Correspondence to Edward J. Mayeaux, Jr, MD, FAAFP, Department of Obstetrics and Gynecology, Louisiana State University Health Sciences Center, 1501 Kings Highway, Shreveport, LA 71130, USA  
E-mail: EMayeaux@lsuhsc.edu

**Current Opinion in Obstetrics and Gynecology** 2006, 18 (suppl 1):S15–S21

## Abbreviations

**CIN** cervical intraepithelial neoplasia  
**HPV** human papillomavirus  
**VLP** virus-like particle

© 2006 Lippincott Williams & Wilkins  
1040-872X

## HPV-associated disease

Human papillomavirus (HPV) is a small, non-enveloped DNA virus that causes a variety of epithelial neoplasias. More than 100 different types of HPV have been identified and can cause a variety of illnesses from benign hand and foot warts to invasive cervical and anal cancer (Table 1). Nearly 40 HPV types that infect the human genital mucosa have been identified, and are referred to as the sexually transmitted HPV types, or simply HPV [1].

HPV is highly prevalent, with an estimated 20 million people infected in the United States [2]. The incidence of HPV infections is rising, with 6.2 million new infections diagnosed annually [3]. Cumulative prevalence rates are as high as 82%, underscoring the fact that all sexually active individuals are at high risk of acquiring HPV infections and are subject to developing HPV-associated diseases [4]. Risk factors for disease include multiple sexual partners, high parity (five or more pregnancies), smoking, impaired cellular immunity, and a young age at the instigation of sexual relationships [5].

External genital warts occur in more than 1 million people per year, and are almost always caused by low-risk HPV types 6 or 11 [6,7]. Although genital warts are typically benign, psychosocial concerns associated with the diagnosis of a sexually transmitted disease (STD) often causes emotional distress in both men and women [8]. Infection with low-risk HPV has also been associated with abnormal Papanicolaou (Pap) test results, and HPV DNA has been found in cervical intraepithelial neoplasia grades 1 and 2 (CIN 1/2) [9]. In addition, infection with HPV types 6 or 11 can cause condylomatous changes that result in serious illness when associated with respiratory laryngeal papillomatosis or occlusive esophageal warts [10].

Infection with high-risk HPV types is associated with many anogenital cancers, including anal, vaginal, vulvar, penile, and cervical cancer [11]. HPV DNA has been found in 99.7% of cervical cancers, and persistent infection with high-risk HPV types is considered necessary, but not sufficient, for developing cervical cancer [12]. HPV 16 alone is responsible for 52% of all cervical cancers [5]. HPV 18 and HPV 16 and 18 coinfection account for another 18% of cervical cancer diagnoses; therefore, HPV 16 and 18 are cumulatively responsible for approximately 70% of all cervical cancer [13]. Epidemiological studies

**Table 1** Locations and lesions associated with HPV infection

Location/lesion	HPV types
Hand and plantar warts	1, 2, 4
Flat warts	3, 10
Butcher's warts	2, 7
Genital warts	6, 11
Periungual warts	16, 18
Oral warts	6, 11
Focal oral epithelial hyperplasia (Heck's disease)	13, 32
Mouth, throat, tongue, and lung cancers	16, 18
Esophageal warts, squamous and glandular esophageal cancers	6, 16, 18, 66, 52
Conjunctival papillomas and carcinomas	6, 11, 16, 18
Cervical, vaginal, vulvar, anal, penile, scrotal, and perineal warts	6, 11
Cervical, vaginal, vulvar, anal, penile, and scrotal cancers	16, 18

HPV = Human papillomavirus.

suggest that infection with HPV 16 or HPV 18 is associated with a more than 400- or 200-fold increased risk of developing cervical cancer, respectively [13]. After reviewing many years of accumulated evidence, both the National Toxicology Program (NTP) and the International Agency for Research on Cancer (IARC) have recognized the oncogenic potential of high-risk HPV types, and officially labeled HPV as a known human carcinogen [14,15].

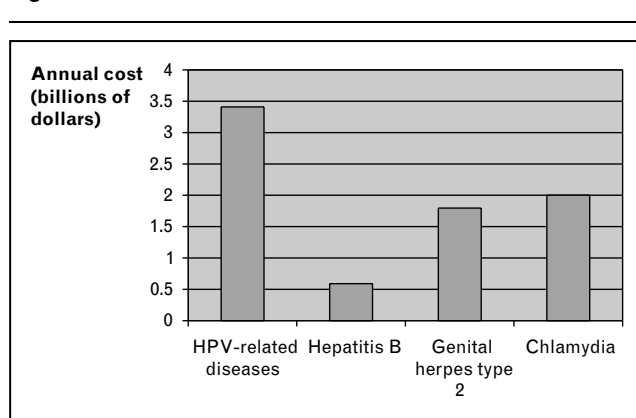
The risks associated with HPV infection are generally not adequately recognized by health care providers or the general public. The proportion of cervical cancer cases attributed to HPV is higher than that of lung cancer cases attributed to smoking tobacco, a setting in which billions of dollars are spent in support of antismoking efforts annually; however, studies have reported that as few as 13–67% of adolescents have ever heard of HPV [16–18].

**The economic burden of HPV infection**

The economic impact of HPV is substantial, including costs for cervical cancer screening, the follow-up of abnormal Pap test results, and treatment for invasive cancer. In an epidemiological study of 103 476 female enrollees of a northwestern US health care insurer, annual cervical HPV-related prevention and treatment costs were estimated to be US\$26 415 in 1998 (per 1000 women, expressed in 2002 US dollars) [19]. Extrapolating this value to the general US population, the cost of HPV infection and its cervical-associated disease sequelae is estimated to be US\$3.4 billion per year [19]. This makes the economic burden of HPV greater than that of hepatitis B, genital herpes, or chlamydia infections (Fig. 1) [19–22].

Only 10% of this estimate, or approximately US\$350 million, is attributed to the treatment of invasive cervical cancer, whereas the other 90% of expenditures is for

**Figure 1** Annual cost of common STD



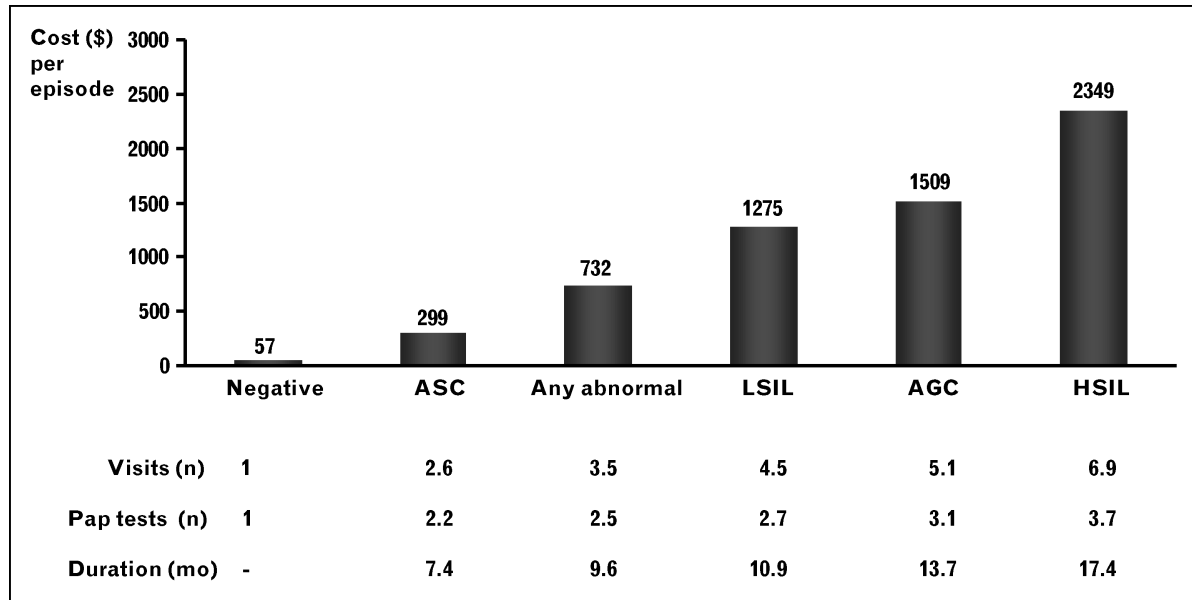
Human papillomavirus (HPV)-related costs are estimated to be US\$3.4 billion per year, making HPV infection more costly than hepatitis B, genital herpes, or chlamydia infections [19–22].

cervical cancer prevention (including the treatment of precancerous lesions and routine Pap screening). Routine cervical cytology amounts to 63.4% of the preventative costs, and false-positive Pap test results account for 9.1% of cervical HPV-related costs [19]. Additionally, substantial costs are associated with routine screening for, and management of, cervical HPV infection (Fig. 2) [19]. When considering positive results, 17.5% of the previously mentioned health plan costs were for the management of cervical precancers. Estimated expenditures were US\$600 million for low-grade and US\$250 million for high-grade squamous intraepithelial lesions [19]. The cost of HPV-related disease would be higher if indirect nonmedical costs, such as lost work time, increased stress and its effects, and lost personal time were included.

The estimated prevalence of HPV in adolescents and young adults 15–24 years old is 9.2 million; in 2000, 4.6 million incident HPV infections occurred in this age group [3]. Thus it is not surprising that young women incur the greatest cost for HPV-related health care. Women aged 20–29 years old incur annual costs (per 1000 women) of US\$51,863, compared with US\$40,967 for women 30–49 years old, US\$28,491 for women 50–69 years old, and US\$14,699 for women 70 years and older [19]. In one study, among both men and women 15–24 years old, approximately US\$2.9 billion was spent in 2000 on the direct medical costs and clinical sequelae associated with cervical abnormalities and external genital warts [23]. This figure was comparable with the cost associated with the treatment of HIV in this age group, estimated to be approximately US\$3 billion in 2000 [24,25].

Diagnosis and treatment of genital warts alone are also very expensive. In 2000, the annual total direct cost associated with anogenital warts for all age groups was US\$167.4 million [23]. Individual episodes of genital

**Figure 2 Health care costs of cervical HPV infection**



In a study of 103 476 female patients, Insinga *et al.* [19] reported a trend of increasing costs associated with increasing grades of initial cytological abnormality. Similar cost trends were reported for number of physician visits and the duration of each episode. Average age adjusted to the 1998 US female population; all cost estimates in 2002 dollars. AGC = Atypical glandular cell; ASC = atypical squamous cell; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion.

warts involve 3.1 physician visits and cost approximately US\$436 (US\$135 per visit) for complete clearance [26]. Moreover, the economic burden of genital warts among young adults is more than 2 times higher than for older age groups [26].

Although the screening and treatment for cervical cancer and its precursors are costly, Pap testing has significantly reduced the mortality rates associated with cervical cancer in developed countries. Nonetheless, cervical cancer screening programs are not accessible to women of all social and ethnic backgrounds. Thus implementation of a cost-effective public health strategy that reduces the risk of cervical cancer in all women is a priority. Vaccination against HPV would be expected to avert some of the costs of the screening and treatment for HPV-related diseases. [Overall, costs associated with HPV infection are so great that even small reductions in its incidence could lead to considerable cost savings.]

**HPV vaccines for prevention of infection**

Vaccines that protect against the most prevalent disease-causing HPV types would be expected to reduce the incidence of the majority of HPV-associated diseases. Vaccine-induced immunity may also reduce both horizontal (person-to-person) and vertical (mother-to-newborn) transmission by reducing or eliminating viral load in infected individuals and preventing progression of low- and high-grade cervical lesions to invasive cancers [27].

During HPV infection, the late (L) genes L1 and L2 are expressed in differentiated superficial squamous cells and encode the capsid proteins that form the mature virion [27]. The major capsid protein L1 comprises the outermost layer of the virus and is important for virion assembly and structure [28]. The exogenous expression of L1 in a variety of cell types, including bacterial, yeast, insect, or mammalian cells, induces the formation of self-assembling virus-like particles (VLPs) that closely mimic the structure of natural HPV virions [28,29]. Because VLPs do not contain genetic material, are not infectious, and have no oncogenic potential, they are ideal candidates for use in preventative HPV vaccines. To prepare a standard vaccine dose of 0.5 ml, VLPs are expressed in yeast or insect cells, purified, concentrated, distributed in 10-µg to 50-µg aliquots per HPV type, and combined with adjuvant [30].

Infection with HPV types 16 or 18 is responsible for approximately 75% of all CIN lesions and 70% of cervical cancers. HPV types 6 and 11 cause nearly all genital warts [31,32]. Consequently, vaccines in clinical development have focused on some or all of these four HPV types. Researchers at the National Cancer Institute conducted the first proof-of-principle HPV type 16 VLP vaccine trial in animal models. They found that the vaccine induced considerable immunity against L1 capsid protein [33,34]. The vaccine was subsequently shown to induce strong humoral immune responses in humans [35]. Moreover, VLP vaccines were shown to be safe, well tolerated, and

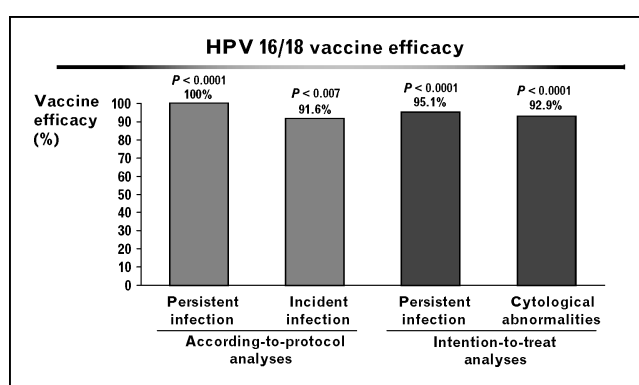
to induce seroconversion in all recipients. In other early trials, after 3 doses of vaccine, recipients exhibited robust B-cell responses and L1-specific T-cell responses with measurable cell-mediated immunity in the cervical mucosa, suggesting that VLP vaccines will effectively prevent HPV infection and HPV-associated disease [35–37].

The first phase 2 study of a proof-of-principle HPV 16 vaccine produced in a large-scale setting confirmed that HPV VLPs induce antibody titers that are significantly higher than those produced by natural infection [38]. No safety issues were documented, and the vaccine was well tolerated. Although the study was not powered to assess efficacy in preventing clinical disease, vaccine recipients developed fewer HPV 16-related cervical lesions than did placebo recipients, and the vaccine was shown to be 100% effective in preventing persistent infection [38]. Other monovalent VLP vaccines have produced similar results [7,39,40].

Immune responses to HPVs are type-specific, so vaccination against multiple HPV types will achieve the greatest public health benefit. Multivalent vaccines incorporating the most common disease-causing HPV types are now in development. A double-blind, placebo-controlled phase 2 trial evaluated the efficacy, safety, and immunogenicity of a bivalent HPV 16 and 18 VLP vaccine in more than 1000 women (15–25 years old) with no history of abnormal cytology and few opportunities for prior HPV exposure [41]. Women were given intramuscular injections of vaccine (20 µg of each VLP plus adjuvant) or placebo (adjuvant alone) on day 1, at month 1, and at month 6, and followed for at least 18 months. Similar to monovalent vaccines, the vaccine was well tolerated, produced no serious adverse events, resulted in seroconversion among the majority of recipients, and induced high titers of type-specific antibodies to both HPV 16 and HPV 18. At the trial’s conclusion, the vaccine was reported to be more than 90% effective in preventing incident, and 100% effective in preventing persistent, infection in vaccine recipients who followed the trial protocol (Fig. 3). Analysis of a modified cohort of women who did not strictly follow the protocol (intention-to-treat analysis), often described as the ‘real world group’, showed that the vaccine protected against more than 85% of persistent infections, and was approximately 93% efficacious in preventing vaccine-type cytological abnormalities [41] (Fig. 3).

A double-blind, placebo-controlled efficacy, safety, and immunogenicity phase 2 study of a quadrivalent vaccine engineered to protect against infection with HPV types 6, 11, 16, and 18 was also conducted. This vaccine, which includes the four most common HPV disease-causing types, is predicted to prevent the majority of genital warts, genital neoplasias, and cervical cancers. More than

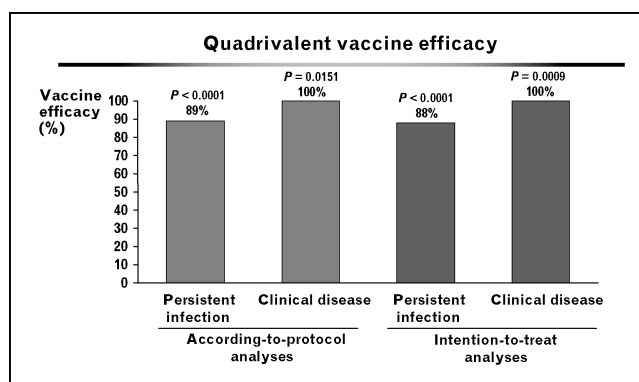
**Figure 3 Efficacy of a bivalent vaccine in preventing HPV-related disease**



Participating women were naive to human papillomavirus (HPV) infection at enrollment and received at least one dose of vaccine. During the 27-month follow-up, the combined incidence of persistent infection was reduced by 95.1%, and the incidence of HPV-related disease was reduced by 92.9% in the intention-to-treat cohort [41].

500 women (16–23 years old), each with fewer than five male sexual partners and no history of abnormal Pap test results, were randomly assigned to receive vaccine (20 µg each of HPV 6 and 18 VLP, and 40 µg each of HPV 11 and 16 VLP plus adjuvant) or placebo (adjuvant only) on day 1, at month 2, and at month 6, and followed for 36 months [42]. The quadrivalent vaccine was also well tolerated, produced no serious adverse events, resulted in complete seroconversion among all recipients, and induced high titers of type-specific antibodies to all four HPV types. In the per-protocol cohort, the vaccine was 89% effective in preventing persistent infection and 100% effective in preventing clinical disease associated with the four HPV types (Fig. 4). Vaccine efficacy in

**Figure 4 Efficacy of a quadrivalent vaccine in preventing HPV-related disease**



Participating women were naive to human papillomavirus (HPV) infection at enrollment and received at least one dose of vaccine. During the 30-month follow-up, the combined incidence of persistent infection was reduced by 88%, and the incidence of HPV-related disease was reduced by 100% in the modified intention-to-treat cohort. Moreover, the incidence of CIN was eliminated in vaccine recipients. The overall efficacy in the modified intent-to-treat cohort was thus 89% [42].

women who did not strictly follow the protocol was also high. In this group, the vaccine was 88% effective in preventing persistent infection, and 100% effective in preventing CIN and other clinical disease (Fig. 4) [42].

Other randomized, placebo-controlled clinical trials are examining the primary endpoints of antibody titers, the prevention of persistent HPV infection, the prevention of abnormal cytology due to the involved HPV types, and the development of CIN and other vaccine type-specific genital lesions. Large natural history studies will add to the knowledge of HPV vaccine behavior over time [43,44]. These studies will determine whether HPV-type substitution infections, variant migration within specific vaccine types, or the increasing virulence of type-specific HPV infections will occur. Additional trials are underway to evaluate the efficacy of HPV vaccination in men and women younger than 15 years and older than 25 years. Recently, the results of the Females United to Universally Reduce Endo-ectocervical disease (FUTURE II) trial were released. The quadrivalent HPV vaccine was found 100% effective at preventing HPV 16- and 18-related CIN 2/3, AIS, and cervical cancer for two years of follow-up [45].

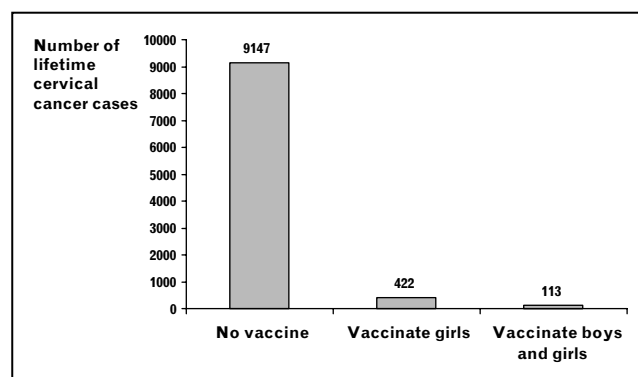
### Public health benefits of HPV vaccination

The potential public health benefits of HPV vaccination have been reported by several mathematical modeling studies, each reporting similar findings [46–48]. A hypothetical vaccine administered to the current US population of 12-year-old girls (approximately 1 988 600), which is 75% efficacious against preventing high-risk HPV infection and requires a booster vaccination every 10 years, was predicted to avert 224 255 HPV infections, 112 710 cases of cervical dysplasia, 3317 cases of cervical cancer, and 1340 cervical cancer-related deaths over the girls' lifetimes [46].

A separate study reported that the vaccination of 12-year-old girls with an HPV 16/18 vaccine would reduce the number of cervical cancer cases caused by HPV 16 or 18 by more than 95% (Fig. 5) [48]. Vaccinating both men and women was predicted to be more beneficial than vaccinating only women in a model that assumed 90% coverage with an HPV 16 vaccine and 75% efficacy in preventing HPV 16 infections for an average of 10 years [47].

Vaccines that effectively reduce the incidence of HPV-associated clinical disease will also reduce the psychological morbidity associated with diagnosis and treatment. A diagnosis of genital warts, an abnormal Pap test result, or cervical cancer can cause high levels of anxiety and emotional distress. Genital warts are often the most anxiety-provoking outcome of HPV infection, especially in sexually active men and women who are not

**Figure 5 Projected reductions in lifetime cervical cancer rates for a theoretical cohort of 12-year-old girls receiving a HPV 16/18 vaccine**



Assuming that 70% of girls were vaccinated, and that the vaccine was 90% efficacious in preventing cervical cancer, a 95.4% reduction was seen in the number of expected lifetime cervical cancer cases that were caused by HPV 16 or 18. Vaccinating both boys and girls was predicted to reduce the incidence of cervical cancer an additional 3.4% [48].

in monogamous relationships [49]. Therefore, vaccination against the most common HPV types that cause genital warts and cervical cancer is expected to eliminate a substantial proportion of the HPV-associated disease burden.

### Vaccination strategies

In order for the vaccines to fully reach their disease prevention potential, public health officials will need to prepare strategies to effectively disseminate HPV vaccines. Vaccination programs must address the timing and route of vaccine administration, appropriate vaccination candidates, the need for boosters, and, potentially overcome social barriers to vaccine acceptance. Recommendations from professional societies, acceptance among health care providers, and strong public educational initiatives will most likely be required for widespread vaccine acceptance.

Vaccination strategies should target both men and women because the primary mode of HPV transmission involves men, and mathematical models suggest that vaccinating men will reduce the incidence of cervical cancer. Vaccination coverage of women will likely be less than 100% and possibly (albeit rarely) ineffective; therefore, vaccination of men would be expected to provide additional protection for the remainder of the female population through herd-immunity effects. A population-level study estimated that a female-only vaccination strategy would probably be only 60–75% as efficient in reducing the prevalence of HPV infection as a strategy targeting both sexes [47]. Precedence for vaccinating men in this setting exists with the rubella vaccine recommendations. Congenital rubella syndrome occurs in children of women who contract rubella during

pregnancy. Although rubella causes no serious morbidity or mortality in males, it causes severe harm to unborn fetuses. Vaccinating both sexes at birth has led to a marked decrease in the incidence of the congenital rubella syndrome [50]. With the use of a quadrivalent vaccine, men would also directly benefit from the prevention of external genital warts.

Because HPV vaccines are prophylactic, vaccination before exposure to HPV will yield the greatest benefit. Vaccines that protect against sexually transmitted infections are ideally administered to a young population that is not yet sexually active. Therefore, the vaccination of adolescents 10–12 years old should provide the most effective control of HPV infection and disease, as this population is generally sexually naive and has been shown to develop vigorous immune responses to vaccines [51]. Furthermore, public health analyses have shown that vaccines are more effective when initiated in younger populations [52]. Experts in adolescent medicine have suggested creating an adolescent immunization platform that could contain meningococcal, hepatitis A, hepatitis B, HPV, and, ultimately, herpes simplex and HIV vaccines. Direct-to-consumer television advertisements currently promote adolescent meningococcal vaccination in some regions of the United States, setting the stage for the acceptance of adolescent vaccination schedules.

## Conclusion

Historically, vaccines have provided an effective means to reduce or even eliminate infectious disease-associated morbidity and mortality. For an HPV vaccine to be efficacious, it must confer durable protection against multiple HPV types. Phase 2 trial results with both a bivalent and quadrivalent vaccine have confirmed that HPV VLP vaccines are safe, effective, and induce long-term immunity to HPV infection. The bivalent vaccine is expected to reduce cervical cancer rates because it protects against HPV 16 and 18. The quadrivalent vaccine protects against HPV 6, 11, 16 and 18, and is expected to reduce the incidence of external genital warts in addition to preventing cervical cancer. Long-term follow-up studies of immunized individuals may also help define the pathological significance of certain HPV types for which the causal relationship is less well understood (e.g. head and neck cancers). To be most effective, HPV vaccines must be administered prior to sexual activity and although women are most at risk, vaccinating both men and women may provide the greatest reduction in HPV-associated disease rates.

## References

- Herrero R, Hildesheim A, Bratti C, *et al.* Population-based study of human papillomavirus infection and cervical neoplasia in rural Costa Rica. *J Natl Cancer Inst* 2000; 92:464–474.
- Cates WJ. Estimates of the incidence and prevalence of sexually transmitted diseases in the United States. American Social Health Association Panel. *Sex Transm Dis* 1999; 26 (suppl 4):S2–S7.
- Weinstock H, Berman S, Cates W Jr. Sexually transmitted diseases among American youth: incidence and prevalence estimates. *Perspect Sex Reprod Health* 2004; 36:6–10.
- Brown DR, Shew ML, Qadadri B, *et al.* A longitudinal study of genital human papillomavirus infection in a cohort of closely followed adolescent women. *J Infect Dis* 2005; 191:182–192.
- Bosch FX, de Sanjose S. Chapter 1: Human papillomavirus and cervical cancer-burden and assessment of causality. *J Natl Cancer Inst Monogr* 2003; 31:3–13.
- von Krogh G. Management of anogenital warts (condylomata acuminata). *Eur J Dermatol* 2001; 11:598–603; quiz 604.
- Brown DR, Bryan JT, Schroeder JM, *et al.* Neutralization of human papillomavirus type 11 (HPV-11) by serum from women vaccinated with yeast-derived HPV-11 L1 virus-like particles: correlation with competitive radioimmunoassay titer. *J Infect Dis* 2001; 184:1183–1186.
- Harper DM. Why am I scared of HPV? *CA Cancer J Clin* 2004; 54:245–247.
- Koutsky LA, Galloway DA, Holmes KK. Epidemiology of genital human papillomavirus infection. *Epidemiol Rev* 1988; 10:122–163.
- Armstrong LR, Preston EJ, Reichert M, *et al.* Incidence and prevalence of recurrent respiratory papillomatosis among children in Atlanta and Seattle. *Clin Infect Dis* 2000; 31:107–109.
- Schiffman M, Kjaer SK. Chapter 2: Natural history of anogenital human papillomavirus infection and neoplasia. *J Natl Cancer Inst Monogr* 2003; 31:14–19.
- Walboomers JM, Jacobs MV, Manos MM, *et al.* Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999; 189:12–19.
- Munoz N, Bosch FX, de Sanjose S, *et al.* Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 2003; 348:518–527.
- National Toxicology Program DHHS. The report on carcinogens. Washington DC: Federal Register 2005; 70.
- IARC working group. IARC monographs on the evaluation of carcinogenic risks to humans: human papillomaviruses. Lyon, France: International Agency for Research on Cancer 1995; 64.
- Franco EL, Harper DM. Vaccination against human papillomavirus infection: a new paradigm in cervical cancer control. *Vaccine* 2005; 23:2388–2394.
- Dell DL, Chen H, Ahmad F, Stewart DE. Knowledge about human papillomavirus among adolescents. *Obstet Gynecol* 2000; 96:653–656.
- Holcomb B, Bailey JM, Crawford K, Ruffin MT. Adults' knowledge and behaviors related to human papillomavirus infection. *J Am Board Fam Pract* 2004; 17:26–31.
- Insinga RP, Glass AG, Rush BB. The health care costs of cervical human papillomavirus-related disease. *Am J Obstet Gynecol* 2004; 191:114–120.
- The Kaiser Family Foundation and the American Social Health Association. Sexually transmitted diseases in America: how many cases and at what cost? Menlo Park, CA: Kaiser Family Foundation; 1998.
- Fisman DN, Lipsitch M, Hook EW, Goldie SJ. Projection of the future dimensions and costs of the genital herpes simplex type 2 epidemic in the United States. *Sex Transm Dis* 2002; 29:608–622.
- Eng TR, Butler WT, editors. Institute of Medicine: Division of Health Promotion and Disease Prevention. Hidden epidemic: confronting sexually transmitted diseases. Washington (DC): National Academy Press; 1997.
- Chesson HW, Blandford JM, Gift TL, *et al.* The estimated direct medical cost of sexually transmitted diseases among American youth. *Perspect Sex Reprod Health* 2004; 36:11–19.
- Kulasingam SL, Harper DM, Meyers ER. Paper presented at: International HPV Conference. Paris, France, 2002.
- Mandelblatt JS, Lawrence WF, Womack SM, *et al.* Benefits and costs of using HPV testing to screen for cervical cancer. *JAMA* 2002; 287:2372–2381.
- Insinga RP, Dasbach EJ, Myers ER. The health and economic burden of genital warts in a set of private health plans in the United States. *Clin Infect Dis* 2003; 36:1397–1403.
- Lowy DR, Frazer IH. Chapter 16: Prophylactic human papillomavirus vaccines. *J Natl Cancer Inst Monogr* 2003; 111–116.
- Zhou J, Sun XY, Stenzel DJ, Frazer IH. Expression of vaccinia recombinant HPV 16 L1 and L2 ORF proteins in epithelial cells is sufficient for assembly of HPV virion-like particles. *Virology* 1991; 185:251–257.

- 29 Hagensee ME, Yaegashi N, Galloway DA. Self-assembly of human papillomavirus type 1 capsids by expression of the L1 protein alone or by coexpression of the L1 and L2 capsid proteins. *J Virol* 1993; 67:315–322.
- 30 Schiller JT, Davies P. Delivering on the promise: HPV vaccines and cervical cancer. *Nat Rev Microbiol* 2004; 2:343–347.
- 31 The Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study (ALTS) Group. Human papillomavirus testing for triage of women with cytologic evidence of low-grade squamous intraepithelial lesions: baseline data from a randomized trial. *J Natl Cancer Inst* 2000; 92:397–402.
- 32 Brown DR, Schroeder JM, Bryan JT, *et al*. Detection of multiple human papillomavirus types in condylomata acuminata lesions from otherwise healthy and immunosuppressed patients. *J Clin Microbiol* 1999; 37:3316–3322.
- 33 Suzich JA, Ghim SJ, Palmer-Hill FJ, *et al*. Systemic immunization with papillomavirus L1 protein completely prevents the development of viral mucosal papillomas. *Proc Natl Acad Sci U S A* 1995; 92:11553–11557.
- 34 Jansen KU, Rosolowsky M, Schultz LD, *et al*. Vaccination with yeast-expressed cottontail rabbit papillomavirus (CRPV) virus-like particles protects rabbits from CRPV-induced papilloma formation. *Vaccine* 1995; 13:1509–1514.
- 35 Pastrana DV, Vass WC, Lowy DR, Schiller JT. NHPV16 VLP vaccine induces human antibodies that neutralize divergent variants of HPV16. *Virology* 2001; 279:361–369.
- 36 Nardelli-Haeffliger D, Wirthner D, Schiller JT, *et al*. Specific antibody levels at the cervix during the menstrual cycle of women vaccinated with human papillomavirus 16 virus-like particles. *J Natl Cancer Inst* 2003; 95:1128–1137.
- 37 Harro CD, Pang YY, Roden RB, *et al*. Safety and immunogenicity trial in adult volunteers of a human papillomavirus 16 L1 virus-like particle vaccine. *J Natl Cancer Inst* 2001; 93:284–292.
- 38 Koutsky LA, Ault KA, Wheeler CM, *et al*. A controlled trial of a human papillomavirus type 16 vaccine. *N Engl J Med* 2002; 347:1645–1651.
- 39 Ault KA, Giuliano AR, Edwards RP, *et al*. A phase I study to evaluate a human papillomavirus (HPV) type 18 L1 VLP vaccine. *Vaccine* 2004; 22:3004–3007.
- 40 Fife KH, Wheeler CM, Koutsky LA, *et al*. Dose-ranging studies of the safety and immunogenicity of human papillomavirus type 11 and type 16 virus-like particle candidate vaccines in young healthy women. *Vaccine* 2004; 22:2943–2952.
- 41 Harper DM, Franco EL, Wheeler C, *et al*. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet* 2004; 364:1757–1765.
- 42 Villa LL, Costa RL, Petta CA, *et al*. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol* 2005; 6:271–278.
- 43 Herrero R, Schiffman MH, Bratti C, *et al*. Design and methods of a population-based natural history study of cervical neoplasia in a rural province of Costa Rica: the Guanacaste Project. *Rev Panam Salud Publica* 1997; 1:362–375.
- 44 Bratti MC, Rodriguez AC, Schiffman M, *et al*. Description of a seven-year prospective study of human papillomavirus infection and cervical neoplasia among 10000 women in Guanacaste, Costa Rica. *Rev Panam Salud Publica* 2004; 15:75–89.
- 45 Skjeldestad FE, FUTURE II steering committee. Prophylactic quadrivalent human papillomavirus (HPV) (types 6, 11, 16, 18) L1 virus-like particle (VLP) vaccine (Gardasil™) reduces cervical intraepithelial neoplasia (CIN) 2/3 risk. Presented at: Infectious Disease Society of America, 2005. San Francisco, Calif.
- 46 Sanders GD, Taira AV. Cost-effectiveness of a potential vaccine for human papillomavirus. *Emerg Infect Dis* 2003; 9:37–48.
- 47 Hughes JP, Garnett GP, Koutsky L. The theoretical population-level impact of a prophylactic human papilloma virus vaccine. *Epidemiology* 2002; 13:631–639.
- 48 Taira AV. Evaluating human papillomavirus vaccination programs. *Emerg Infect Dis* 2004; 10:1915–1923.
- 49 Baer H, Allen S, Braun L. Knowledge of human papillomavirus infection among young adult men and women: implications for health education and research. *J Commun Health* 2000; 25:67–78.
- 50 Wexler D editor. Needle tips and the hepatitis B coalition news. St Paul, MN: The Immunization Action Coalition; 2004.
- 51 Sexually transmitted infections quarterly report: anogenital warts and HSV infection in England and Wales. *Communicable Dis Rep* 2001; 11: 11–15.
- 52 Jansen KU, Shaw AR. Human papillomavirus vaccines and prevention of cervical cancer. *Annu Rev Med* 2004; 55:319–331.