



Kathleen Buetow, MD, DrPH

## Human Papillomavirus Vaccines

### Introduction

Human papillomaviruses (HPVs) are a group of small DNA viruses that infect stratified squamous epithelial cells in different parts of the body. More than 100 types have been identified. These viruses can be subdivided into cutaneous HPV, which cause hand and plantar warts, and mucosal HPV which can infect mucosal and cutaneous surfaces of the anogenital tract. There are at least 40 types of mucosal HPV which can further be subdivided into low and high risk oncogenicity. HPV genital infections are generally asymptomatic and clear spontaneously. However, they vary in effect from benign anogenital warts to invasive cancer.<sup>1</sup>

### Prevalence of HPV

HPV is the most common sexually transmitted disease (STD) in the world, infecting 20 million in the US alone, with a worldwide incidence of 440 million. There are 6.2 million new infections per year in the US. Low risk HPV (types 6, 11) cause anogenital warts and low-grade cervical intraepithelial neoplasia (CIN). High risk HPV (types 16, 18 and others) are associated with high-grade CIN. Types 16 and 18 cause about 70% of cervical cancers, the second most common cancer in women.<sup>2-6</sup>

There is a lifetime HPV incidence of 70–80%; however, infection with HPV frequently develops soon after the initiation of sexual activity with studies indicating 30% of women acquired the infection within the first year of the onset of genital contact and 50% within the first four years of sexual activity.<sup>7</sup> HPV can be spread by skin to skin contact in addition to true sexual penetration. Infection rates are highest in adolescents and decrease with age. One in four women aged 15–24 have acquired an HPV infection. Prevalence rates of HPV in males are less well-defined.

**Table 1.<sup>8</sup> The Prevalence of High Risk HPV by Age: n = (8426)**

Age Group - Years	HR-HPV Prevalence %
14–19	25%
20–29	22%
30–39	12%
40–49	11%
50–65	6%

HPV infections are generally transient. Only 3–10% of females with persistent infection with high risk HPV get cervical cancer. There are 12,000 cases of cervical cancer diagnosed each year and 4000 deaths from cervical cancer per year in the US. HPV 16 accounts for about 50–60% of cervical cancer while HPV 18 is responsible for 13–16% of cervical cancer.<sup>1,2</sup>

**Table 2.<sup>9</sup> HPV Types and the Clinical Sequelae**

HPV Types (~100):

- Cutaneous
- Mucosal (anogenital, aerodigestive)
  - Low risk 6, 11
    - Genital warts
    - Recurrent respiratory papillomatosis
  - High risk 16, 18, 31, 33, 35, 45, 59, 66
    - Cervical dysplasia, cancer
    - Other anogenital cancers
    - Oral, esophageal cancers

There are many consequences of HPV. HPV is responsible for over 1 million cases of genital warts per year. HPV results in 1.4 million cases per year of CIN–1 and 333,000 cases of CIN–2 –3 per year. With over 1 million abnormal pap tests per year attributable to HPV, there are associated increased costs as well as significant anxiety for the patient.

Additional testing, which may include colposcopy → cervical scraping → biopsy → hysterectomy, are directly linked to the presence of HPV. The estimated cost of HPV is 2.8 billion per year in the US alone.<sup>10-14</sup>

### Adolescents and HPV

Adolescents are at increased risk of acquiring HPV infection due to several factors. Complete epithelialization of the cervix does not occur until adulthood. Immature cervical tissue predisposes the adolescent to HPV. Also, women who engage in sexual activity before 17–18 years of age have three to four times the risk of developing cervical cancer. Current statistics on adolescent sexual behavior show the mean age for first intercourse to be 16–17 years of age with one third of teens initiating sex by 9th grade and 10% of 9th graders having had more than four partners.<sup>7,15</sup>

**Table 3. Risk Factors for Acquiring HPV**

- Early age at onset of sexual activity
- Number of sexual partners
- Partner's number of sexual partners
- Cigarette usage
- Immunocompromised individuals
- Presence of other STDs
- Individuals with a rheumatologic disorder
- Long-term oral contraceptive use
- Parity
- Cervical ectopy

### HPV Prevention

Through genetic engineering of HPV types, it was possible to construct a non-infectious virus-like particle that retains the antigenicity necessary to induce neutralizing antibodies. Currently there are two vaccines that have demonstrated efficacy against oncogenic strains of HPV. Merck has produced a Quadrivalent HPV Vaccine (types 6, 11, 16, 18) Recombinant Vaccine (Gardasil®) that shows a 90% efficacy against persistent cervical HPV and genital warts; GlaxoSmithKline (GSK) has developed Cervarix™\* (types 16 and 18) which is also highly immunogenic against cervical HPV infection.<sup>9</sup>

### Evaluation of Vaccines

The Merck-developed vaccine known as Gardasil® has been tested in >20,000 women

\*At the time of this writing Cervarix™ is not on the market; however, it is in the final stages for approval by the FDA.

and GSK's Cervarix™ in >30,000 women. These vaccines were 90–100% effective against the HPV types tested. Both had minimal side effects, mainly discomfort at the injection site. Gardasil® was approved by the Food and Drug Administration (FDA) in June 2006 and recommended by the American Committee on Immunization Practices (ACIP) June 29, 2006. Provisional recommendations were published by the CDC on August 14, 2006 with final recommendations expected to be published in MMWR within a few months.<sup>11</sup>

**Table 4.<sup>11</sup> Recommendations for Administering Gardasil®**

- Females aged 11–12 years (primary target)
- May give as young as age nine years
- Catch-up doses to all females 13–26 years old (even if they have been infected with one of the HPV viruses)
- Ideally use the vaccine prophylactically prior to the onset of sexual activity
- Three doses intramuscularly, with a dose given at two months and again at six months after initial dose
- No change in pap scheduling (since vaccine protects against only two of the oncogenic strains – although it covers 70% of infections associated with cervical cancer)
- May be given with Tdap, MCV4
- May be given to patients with genital warts
- May be given to lactating women
- May be given to immunosuppressed individuals

**Table 5.<sup>17</sup> Contraindications of Gardasil®**

- Sensitivity to yeast
- Sensitivity to vaccine component
- Pregnancy (if given to pregnant women, report to vaccine pregnancy registry at 800-986-8999)
- Moderate or severe illness

### Implementation Issues

There are many implementation issues for this vaccine. The required schedule of three doses, initial dose followed by another dose at two and again at six months, is a challenge for patient compliance. The cost of \$360–\$500 per series is prohibitive for many unless private insurances and the Vaccine for Children Program cover the cost. These objective factors alone will cause significant implementation issues.

There are also numerous social and subjective issues surrounding implementation. An STD stigma remains. There is also a fear that by increasing protection there will be a resultant increase in risky sexual behaviors. The increased number of immunizations now due at ages 11–12, including Tdap, meningococcal conjugate vaccine and a possible varicella booster, could create reluctance to add another three injection regime. Also, many parents deny the impending sexuality of their children, or anticipate a late onset of sexual behavior. There may develop resistance to school-based distribution based on cultural or religious beliefs. Since administration of the HPV vaccine will likely require parental consent, it is important that parents become knowledgeable about the nature of the vaccine.

Other challenges remain. Convincing adolescents to accept a vaccine to prevent an illness that will occur later in adulthood will be difficult. There is a lack of general knowledge about HPV which must be overcome with appropriate educational material. Availability to the high risk/low resource population may be limited. Professional willingness to vaccinate young girls might also be lacking without appropriate clinical education.<sup>18</sup> A recent survey of pediatricians found that while most endorsed the vaccine for older adolescents, more than half expressed reluctance in offering it to 10–12 year olds.<sup>19</sup> This survey was completed prior to the ACIP recommendations to target 11–12 year olds and thus may not reflect actual current intentions.

### Conclusion

There is an effective vaccine available to prevent the acquisition of certain common oncogenic strains of HPV. Because HPV is frequently acquired within a few years of onset of sexual activity, and because HPV more frequently affects the adolescent cervix, the most effective use of this vaccine is in the pre-adolescent girl aged 10–12. Pediatricians and others who care for this population must acknowledge the value of administering this vaccine prior to the onset of sexual activity and prepare to adequately inform families of the availability and efficacy of HPV vaccines.

*Kathleen Buetow, MD, DrPH, is a board certified pediatrician at Carle Clinic, Urbana IL and Head of the Department of Pediatrics at the University of Illinois College of Medicine at Urbana-Champaign.*

### References

1. Bonnez W. Immunization against genital human papillomaviruses. *Pediatr Infect Dis J* 2005; 24(11):1005–1006.
2. Cates W Jr. Estimates of the incidence and prevalence of sexually transmitted disease in US. *Sex Transm Dis* 1999;26(4 Suppl): S2–S7.
3. Weinstock H, Berman S, Cates W Jr., Sexually transmitted disease among American youth, incidence and prevalence estimates, 2000. *Perspect Sex Reprod Health* 2004;36(1):6–10.
4. World Health Organization Initiative for Vaccine Research. Viral cancers: human papillomavirus. Available at: <http://www.WHO.Int/Vaccine/Research/diseases/Viral/Cancers/en/index3.html>. Accessed March 7, 2007.
5. Trottier H, Franco E. The epidemiology of human genital human papilloma virus infection. *Vaccine* 2006;24(suppl 1):S1–S15.
6. Center for Disease Control and Prevention – CDC Fact Sheet. Available at: <http://www.cdc.gov/STD/HPV/STDFact-HPV.htm>. Accessed March 7, 2007.
7. Moscicki AB. Impact of HPV infection in adolescent populations. *J Adolesc Health* 2005; 37(6 Suppl):S53–S59.
8. Datta D. HPV surveillance in family practice settings. National Title X Grantee Meeting; 2006 Sept 19; Phoenix, AZ. Available at: [http://www.ent-s-t.com/OFP\\_TitleX\\_Meeting/presentations/306,16,HR-HPV Prevalence by Age Group](http://www.ent-s-t.com/OFP_TitleX_Meeting/presentations/306,16,HR-HPV%20Prevalence%20by%20Age%20Group). Accessed March 13, 2007.
9. Kahn JA, Hillard P. Progress in preventing cervical cancer and other HPV related diseases. *Contemp Pediatr* 2006;23(3):1–7.
10. Insigna RP, Glass AG, Rush BB. The health care costs of human papillomavirus-related disease. *Am J Obstet Gynecol* 2004;191(1):114–120.
11. Kahn JA. Vaccination as a prevention strategy for human papilloma virus related disease. *J Adolesc Health* 2005;37(6 Suppl):S10–16.

12. Schiffman M, Solomon D. Findings to date from the ASCUS–LSIL triage study (ALTS). *Arch Pathol Lab Med* 2003;127(8):946–949.
13. Fleischer AB, Parrish CA, Glenn R, Feldman SR, Condylomata acuminata (genital warts): patient demographics and treating physicians. *Sex Trans Dis* 2001;28(11):643–647.
14. Pichichero M. HPV vaccine is weapon against cervical cancer. *Pediatric News* 2005;39(10):17 (col. 1).
15. Eaton D, Kahn L, Kinchen S, Ross J, Hawkins WA, Lowry R, et al. Youth risk behavior surveillance United States 2005. *MMWR Surveill Summ* 2006;55(5):1–108.
16. ACIP provisional recommendations for the use of quadrivalent HPV vaccine. August 14, 2006. Available at: [http://www.cdc.gov/nip/recs/provisional\\_resc/hpv.pdf](http://www.cdc.gov/nip/recs/provisional_resc/hpv.pdf). Accessed March 7, 2007.
17. HPV and HPV vaccine; information for healthcare providers. Centers for Disease Control 2006. Available at: <http://www.cdc.gov/std/hpv/hpv-vacc-hep-3-pages.pdf>. Accessed March 12, 2007.
18. Zimet GD. Improving adolescent health, focus on HPV vaccine acceptance. *J Adolesc Health* 2005;37(6 Suppl):S17–S23.
19. Daley M, Lidden N, Crane LA, Batey BL, Barrow J, et al. A national survey of pediatrician knowledge and attitudes regarding human papillomavirus vaccination. *Pediatrics* 2006;118(6):2280–2289.

### CME Questions 2a-d

Please select the best answer for the following:

- 2a. Human papillomavirus is the most common sexually transmitted disease. Which statement is correct:
  - a. There are 6.2 million new cases per year in the US.
  - b. Less than 20% of women will have HPV in their lifetime.
  - c. There are 20,000 males who die annually from HPV.
- 2b. A mother asks you if vaccination with HPV vaccine is advisable for her 11-year-old daughter. Your correct information includes:
  - a. HPV is frequently acquired in the first two years of sexual activity.
  - b. Vaccine is best given prior to the onset of sexual activity.
  - c. One in four women age 15–24 has acquired HPV.
  - d. Risk factors for acquiring HPV include early age of onset of sexual activity, multiple partners and smoking.
  - e. Answers A and C are correct.
  - f. All of the above.
- 2c. A mother states that both she and her sisters have had abnormal pap tests. She inquires about HPV vaccine for her 10-year-old daughter. You correctly tell her:
  - a. Any HPV infection increases the risk of cervical cancer.
  - b. Persistent infection increases the risk of cervical cancer.
  - c. Cervical cancer risk is significantly increased if a person has genital warts.
  - d. Her daughter has an increased genetic risk of cervical cancer, even without any HPV exposure.
- 2d. A 16-year-old girl comes to her doctor for an annual physical and she is noted to have a genital wart. She inquires about HPV vaccine. The correct response is:
  - a. The vaccine will cure the genital wart.
  - b. The vaccine is no longer indicated because she already has an HPV infection.
  - c. The vaccine is indicated as a preventative against other strains of HPV.