POSITION STATEMENT

Human Papillomavirus Vaccination: A Case for Mandatory Immunization?

Kristin Klein, PharmD, Sherry Luedtke, PharmD and the Advocacy Committee of the Pediatric Pharmacy Advocacy Group

KEYWORDS human papillomavirus, immunization, pediatrics, vaccination

J Pediatr Pharmacol Ther 2008;13:47-50

The human papillomavirus (HPV) is the most common sexually transmitted disease in the United States, affecting greater than 6 million people annually. The majority of newly infected individuals are between the ages of 15 and 24 years. Although the vaccine may be administered from 9 to 26 years of age, the Centers for Disease Control and Prevention (CDC) currently recommends routine vaccination with the HPV vaccine for females at 11-12 years of age. The Pediatric Pharmacy Advocacy Group endorses the safety and efficacy of the quadrivalent HPV vaccine and agrees that the vaccine should be recommended for all adolescent girls, preferably prior to their "sexual debut." Furthermore, we support the recommendation that young women through the age of 26 years should be vaccinated in order to decrease the risk of contracting a cancer-causing strain of HPV, even if they are already sexually active.

BACKGROUND

Each year, the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) develop and publish their recommended routine pediatric immunization schedule. The recommendations for immunization practice within this schedule are developed based on the risk/benefit for an individual child, as well as the public health benefit at large. These vaccines, which are recommended but not mandated by the CDC, are generally required for enrollment or admission to state-funded schools and day-care centers. Mandates for immunization are usually determined by the state legislatures. Some states do allow parents to decline vaccinations for medical, religious or "conscientious reasons," which may affect immunization coverage rates and potentially negate the impact and overall benefit to the public.

ABBREVIATIONS ACIP, Advisory Committee on Immunization Practices; AAP, American Academy of Pediatrics; CDC, Centers for Disease Control and Prevention; HPV, human papillomavirus; PPAG, Pediatric Pharmacy Advocacy Group; STD, sexually transmitted disease; Tdap; tetanus, diphtheria and reduced acellular pertussis

The decisions to mandate immunizations recommended by the CDC are often influenced by lobbyists, who may not focus on the public health benefits of an immunization policy, but rather focus on things such as religious beliefs, individual rights, and financial concerns. Frequently parents are pulled into the controversy and provided misinformation or partial information, which clouds their ability to make individual decisions for their own children. Such conflicting information is now the case with the new human papillomavirus (HPV) immunization recommendations. At present, numerous state legislatures are wrestling with the decision to mandate HPV vaccination of adolescent females. The fact that HPV vaccination provides protection against

Address correspondence to: Pediatric Pharmacy Advocacy Group, 7975 Stage Hills Blvd Ste 6, Memphis, TN 38133, email: matthew.helms@ppag.org

a sexually transmitted communicable disease adds another level of controversy. This statement attempts to clarify the controversy in an effort to assist parents/guardians in making informed decisions regarding the immunization of their children.

EPIDEMIOLOGY

Human papillomavirus is likely the most common sexually transmitted disease in the United States, with more than 6 million people becoming infected each year.[1,2] Among newly infected cases, 74% are between the ages of 15 and 24 years.[1,2] Persistent infection with HPV is a known risk factor for the development of cervical cancer. In 2003, 100% of the cervical cancers reported to the CDC were positive for a cancer-causing type of HPV, 70% of which were due to HPV types 16 or 18.[2] The CDC estimates that approximately 11,000 women will be diagnosed with cervical cancer this year alone in the United States, with more than 3500 women dying as a result of cervical cancer.[2] Estimates of HPV infection demonstrate that greater than 80% of sexually active women will become infected with HPV by the time they reach the age of 50 years.[1] Although not as commonly isolated, men are also frequently infected with HPV.

The ACIP currently recommends that the HPV vaccine be administered to adolescent girls during their 11-12 year check-up, prior to when most adolescent girls reach their "sexual debut." A survey conducted annually by the CDC evaluating high-risk behaviors in adolescents revealed that in 2005, 62.4% of girls and 63.8% of boys were sexually active by the time they entered 12th grade.[3] Additionally, 3.7% of adolescent girls and 8.8% of adolescent boys reported becoming sexually active before the age of 13.[3] In 2005, 12% of adolescent girls and 16.5% of adolescent boys reported having 4 or more sexual partners, which is another major risk factor for contracting HPV infection.[3]

Each year, approximately US $4 billion is spent on HPV management.[1] The majority of these health-care dollars are spent on follow-up for abnormal Pap smears and on treatment for cervical cancer. Besides the economic burden of HPV infection, a significant emotional burden may occur in a woman with an abnormal Pap smear or who requires a hysterectomy for treatment of cervical cancer.

PATHOPHYSIOLOGY

The human papillomavirus commonly infects the genital tract, but may also infect the respiratory tract of an infant born to an infected mother. It is primarily transmitted via sexual contact, but has been transmitted through direct contact with lesions on the skin. This virus replicates in the squamous epithelial cells and has been associated with cervical cancer as well as other anogenital cancers, anogenital warts, and recurrent respiratory papillomatosis.[2,4] Over 100 strains of HPV have been identified; however, only 40 have been shown to infect the genital tract. Although an acute infection may be clinically evident by the presence of genital lesions or warts, the majority of infected individuals are unaware of their infection and may, thus, transmit it to others.[2,4] Infections with HPV typically resolve without clinical complications within 1 year. Approximately 10%-15% of infections remain persistent, which poses a risk of invasive cervical carcinoma and other anogential carcinomas.[4]

Although relatively few HPV infections lead to cervical cancer, almost all (99%) cervical cancer in women is associated with a previous HPV infection.[1,2,4] Two HPV strains, HPV 16 and 18, have been associated with 70%-80% of "high grade" or precancerous cervical lesions.[2,4] These strains are the primary target for the prevention of cervical cancer in the currently marketed HPV vaccine as well as additional vaccines currently under investigation. In addition, HPV strains 6 and 11 have been associated with more than 90% of all genital warts and approximately 10% of "low grade" or low risk cervical lesions. Thus, vaccination against these strains provides additional benefit.[2] Individuals infected with one strain of HPV are not protected from infections against other strains; therefore, repeated infections can occur throughout one's lifetime.[4]

IMMUNIZATION

Currently only one HPV vaccine, Gardasil (Merck, Whitehouse Station, New Jersey), is commercially available, however, other HPV

vaccines are under development. This vaccine is composed of virus-like particles or proteins from strains 6, 11, 16 and 18 which self-assemble into structures that immunologically resemble surface structures of HPV. The current vaccine, Gardasil, is formulated with an aluminum adjuvant to enhance the immune response to the protein components.[5] Gardasil is frequently referred to as a quadrivalent vaccine because it is composed of virus-like particles from the 4 strains that commonly cause infections (HPV 6, 11, 16 and 18).[5] Gardasil is approved by the FDA for females 9-26 years of age for prevention of cervical cancer, genital warts and some precancerous lesions caused by HPV types 6, 11, 16 or 18.[6] Cervarix (GlaxoSmithKline, Research Triangle Park, North Carolina), an HPV vaccine awaiting FDA approval, only includes HPV strains 16 and 18.[2,5]

As previously mentioned, routine HPV vaccination is recommended for females at 11-12 years of age, although the vaccine may be administered from 9 to 26 years of age.[2] Vaccination involves a 3-dose series administered at baseline, 2 and 6 months.[2,5] Antibody responses to vaccination have been shown to be higher than those observed from natural infection. Vaccination has been shown to be 90% effective in reducing persistent HPV infections and the risk for cervical dysplasia and 99% effective in preventing disease such as genital warts or lesions.[2,4]

Vaccination in early adolescence is recommended to obtain an adequate immune response prior to the sexual debut.[1,2] Long-term immunogenicity following HPV vaccination is unknown; follow-up studies of antibody responses are documented only to 5 years. Antibody concentrations decline during the first 18 months after vaccination then stabilize 3.5 years after vaccination.[2,5] This response is similar to what was observed with the hepatitis B vaccination, for which we know that waning antibody concentrations are not associated with waning immunity. Post-marketing surveillance will determine the need for future booster vaccination.[2,5]

Patients who have been previously infected with at least one type of HPV in the vaccine should still be vaccinated because the vaccine will be effective in preventing infection from the 3 other serotypes in the vaccine.[2,4] The role of HPV vaccination in males is currently under investigation, although studies have shown similar antibody responses compared to females.[5] The societal benefits of male vaccination for the prevention of female infections is yet to be delineated, although some indicate this may not be cost-effective.[4]

CONTROVERSY

Vaccination against HPV is a controversial topic for many reasons, including: 1) safety of vaccines, in general; 2) moral objections; 3) perceived risk of increased promiscuity in adolescents; 4) long-term efficacy of the vaccine; 5) vaccine availability; 6) cost; and 7) gender discrimination.

Following the very real association between the old rotavirus vaccine (Rotashield, Wyeth, Madison, NJ) and intussusception and the unsubstantiated link between the measles, mumps and rubella (MMR) vaccine and autism, the public is much less confident in the safety of vaccines than they used to be. Although we can never be entirely sure that a new vaccine or drug will be completely safe in every person who receives it, safety studies of the quadrivalent HPV vaccine (Gardasil) have not revealed significant adverse effects. The most common adverse effects reported are injection site related (e.g., pain, redness, swelling).

Since the HPV vaccine protects against a sexually transmitted disease (STD), considerable debate regarding the vaccine revolves around the moral implications. People who object to the HPV vaccine on moral grounds usually do so for one of two reasons: 1) fear that providing a vaccine against an STD will increase sexual activity among adolescents, or 2) vaccination is unnecessary since premarital sex is immoral and adolescents should abstain from having sex. Several studies have shown adolescents' sexual activity is not influenced by the availability of condoms or emergency contraception, but has more to do with religious objections and fear of pregnancy.[7] It is important, however, to keep in mind that 6.2% of all adolescents are sexually active by the age of 13 years and 63.1% are sexually active by the time they enter 12th grade.[3] Parents need to be cognizant of this fact when making the decision of whether to vaccinate their children.

From an economic standpoint, the HPV vaccine is fairly costly at US $120 per dose (US $360 for the 3-dose series). Since the vaccine has been added to the recommended childhood immunization schedule, the Vaccines for Children program should cover the cost of the vaccine in eligible adolescents. Many insurers are covering the cost of vaccination for females, but not males, since the vaccine is not approved for use in males.

For practitioners, some additional questions regarding the HPV vaccine still need to be addressed, including those regarding vaccine availability. Now that the vaccine is included in the childhood immunization schedule, will vaccine supply be able to keep up with demand? Availability has become a problem with some vaccines recently, including the Tdap (tetanus, diphtheria and reduced acellular pertussis) and meningococcal conjugate vaccines. The feasibility of achieving complete immunization with the 3-dose series in the adolescent population, which historically is frequently lost to medical follow-up, remains a concern. The long-term efficacy of the quadrivalent vaccine remains unknown. To date, efficacy studies have only followed vaccine recipients for a maximum of 5 years. In the future, will booster doses be required?

RECOMMENDATIONS

The Pediatric Pharmacy Advocacy Group (PPAG) endorses the safety and efficacy of the quadrivalent HPV vaccine and agrees that the vaccine should be recommended for all adolescent girls, preferably prior to their "sexual debut." Furthermore, we agree that the HPV vaccine should be recommended to young women through the age of 26 years to decrease the risk of contracting a cancer-causing strain of HPV, even if they are already sexually active. PPAG acknowledges that the decision to vaccinate an adolescent against HPV is controversial and believes that parents and/or caregivers should be able to choose whether or not to vaccinate their adolescents. As further information becomes available regarding factors such as feasibility of mandatory vaccination and the role of vaccinating males in decreasing HPV transmission, decisions regarding HPV vaccination may become less controversial.

ACKNOWLEDGMENTS Janet Gilsdorf, M.D., who served as chair of the ACIP subcommittee that drafted the HPV guidelines, served as an external reviewer for the position statement.

Members of the PPAG Advocacy Committee included: Elizabeth Boucher, PharmD, Leslie Briar, PharmD, Margaret Burke, PharmD, Cathy Crill, PharmD, Brian Cowles, PharmD, Cindy Dusik, PharmD, Helen Fiechtner, PharmD, Shawn Gillikin, PharmD, Peter Johnson, PharmD, Bernard Lee, PharmD, Lisa Lubsch, PharmD, Bradley McCrory, PharmD, Amy Mitchell, PharmD, Kimberly Novak, PharmD, Leslie Patatanian, PharmD, Kathy Pham, PharmD, Joan Reilly, PharmD, Tara Smith, PharmD, Catherine Tom, PharmD, and Sharmeen Younas, PharmD

Approved by the PPAG Board of Directors on February 14, 2008, and adopted on February 14, 2008.

REFERENCES

1. Human papillomavirus. Centers for Disease Control and Prevention. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. Atkinson W, Hamborsky J, McIntyre L, Wolfe S, eds. 10th ed. Washington DC: Public Health Foundation, 2007.
2. Centers for Disease Control and Prevention. Quadrivalent human papillomavirus vaccine. Recommendations on the advisory committee on immunization practices. MMWR 2007;56 (RR-2).
3. Centers for Disease Control and Prevention. Youth Risk Behavior Surveillance —United States, 2005. Surveillance Summaries, June 9, 2006. MMWR 2006;55(No. SS-5).
4. Saslow D, Castle PE, Cox JT, et al. American Cancer Society guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. CA Cancer J Clin 2007;57:7-28.
5. Siddiqui MAA, Perry CM. Human papillomavirus quadrivalent (types 6, 11, 16, & 18) recombinant vaccine (Gardasil). Drugs 2006;66:1263-1271.
6. Gardasil [package insert]. Whitehouse Station, NJ; Merck & Co.: July 2007.
7. Kirby D, Brener ND, Brown NL, et al. The impact of condom distribution in Seattle schools on sexual behavior and condom use. Am J Public Health 1999;89:182-187.