

Human Papillomavirus Vaccination—Making a Difference

a report by

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Genital human papillomavirus (HPV) is the most common sexually transmitted infection in the US. It is estimated that 6.2 million people become newly infected annually in the US.¹ Up to 50% of these infections occur in adolescents and young adults between 15 and 24 years of age.² Most HPV infections are asymptomatic or self-limited; however, persistent HPV infections can lead to cervical cancer in women, as well as other anogenital cancers and genital warts in both men and women. Approximately 12,000 women are diagnosed with cervical cancer annually, with a mortality rate of 4,000 women per year in the US.³ Although it is difficult to ascertain, it is estimated that the prevalence of HPV in the anogenital area and in semen is approximately 51% for men 18–40 years of age in the US.⁴ On June 6, 2008, the US Food and Drug Administration (FDA) licensed the use of a quadrivalent human papillomavirus (HPV) vaccine, Gardasil®. It is the first vaccine created that protects against genital warts and certain types of cervical cancer.⁵

Human Papillomavirus

Biology

HPV is a non-enveloped, double-stranded DNA virus belonging to the *Papillomaviridae* family. HPV consists of an 8kb circular DNA strand within a capsid shell. The capsid shell is composed of the major capsid protein L1 and the minor capsid protein L2. Unaccompanied L1 proteins will automatically form empty viral shells that are referred to as virus-like particles (VLPs).⁵ The most specific antibodies in humans have been found to be those directed against L1 capsid proteins assembled as VLPs.⁵ The virus causes infection in the basal layer of the epithelium and

replicates in the epithelial cells. Infected epithelial cells thus remain in an active cell-cycle, resulting in thickened and exophytic lesions. The virus is shed as these epithelial cells are sloughed off. HPV can lead to neoplastic potential through integration into the host genome. There have been over 100 types of HPV identified, of which over 40 have been found to infect the genital area.⁶ The HPV types can be further divided into high-risk and low-risk for malignancy. High-risk types include HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82; low-risk types include HPV-6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108. Types 26, 53, and 66 have been identified as probable high-risk.⁷

Epidemiology

Genital infection with HPV is transmitted by genital contact—primarily by sexual intercourse. The highest-risk factor associated with infection is the number of sexual partners.⁵ Statistical studies have shown that 24% of females in the US are sexually active by 15 years of age, 40% by 16 years of age, and 70% by 18 years of age.⁸ Of the sexually active females, 5.7% of ninth graders and 20.2% of 12th graders have had four or more sexual partners.⁹

Despite the fact that most HPV infections clear spontaneously within two years, some infections progress to cervical cancer. Although infection with HPV is necessary for the development of cervical cancer, infection alone is not sufficient. The key risk factor in the development of cervical cancer is persistent infection with a high-risk type of HPV. HPV-16 has been shown to be the most oncogenic of all high-risk HPV types.^{10,11} Other contributing factors to the progression of cervical cancer include host immune status, cigarette smoking, increased parity, advanced age, other sexually transmitted infections, and obesity.¹²

It has been estimated that over 80% of sexually active women will have acquired genital HPV by 50 years of age.¹³ The prevalence of HPV peaks in females 14–19 years of age and decreases with increasing age. An estimated 20–40% of adults become infected with HPV-16. Infection with HPV occurs soon after initiation of sexual intercourse. One prospective study found the probability of HPV infection to be 38.9% within two years of first sexual intercourse in college women, with the highest rate for HPV-16 infection (10.4%), followed by HPV-18 infection (5.6%).¹⁴

High-risk HPV types are the cause of all cervical cancers, 90% of anal cancers, 40% of vulvar and vaginal cancers, 12% of oropharyngeal cancers, and 3% of oral cancers.¹⁵ HPV types 18 and 16 have also been found in approximately half of all penile cancers. Of the high-risk HPV types that cause cervical cancer, types 16 and 18 are responsible for approximately 70% of all cervical cancers worldwide. Cervical cancer is the second most common cancer in women



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worldwide. It is the 11th most common cancer in women in the US, and the leading cause of cancer-related deaths in many developing countries. It has been estimated that 10,370 new cases of cervical cancer occurred in US women in 2005, and 3,710 deaths in 2005 were attributed to cervical cancer.¹⁶ The majority of cervical cancers in the US are squamous cell, with the rest of them being adenocarcinomas. HPV types 16 and 18 cause almost 70% of those squamous cell cancers and over 80% of the cervical adenocarcinomas.

HPV infection is the cause of all anogenital warts (condyloma accuminata), with the majority caused by HPV types 6 and 11. It takes about two to three months on average to see the development of new anogenital warts after infection with HPV types 6 or 11.¹⁷ Although around one-quarter of anogenital warts regress spontaneously, approximately one-third recur regardless of treatment. It is difficult to know the actual incidence of genital warts, but it is estimated that at least 1% of all sexually active adolescents and adults in the US have clinically visible genital warts.¹⁸

Significantly less is known about HPV infection in males than in females. A wide range of HPV types have been associated with infection of the male genitalia. HPV-6 is the most common HPV genotype associated with male genital warts and HPV-7 is the genotype most frequently associated with penile squamous cell carcinoma. Infection with HPV-16 and HPV-18 is associated with a significantly higher rate of anogenital and oropharyngeal cancers. In males, HPV DNA and RNA have been found in the penile shaft, glans, urethra, ductus deferens, epididymis, testes, and even seminal fluid. The presence of HPV in seminal fluid has also been associated with alterations in sperm parameters, such as volume, viscosity, pH, sperm count, motility, and viability.¹⁹ Due to such effects on sperm parameters, HPV infection has also been reported to decrease male fertility.¹⁹ One particular study illustrated a reduction in sperm motility in the semen samples of patients who had HPV DNA in their sperm pellets.¹⁹ Although it was not proved whether the HPV DNA was integrated into the sperm nucleus or not, there was still a strong association between HPV DNA positivity at the head site and reduced sperm motility (25% of sperm).¹⁹

Human Papillomavirus Vaccines

Currently, the only FDA-approved HPV vaccine is Gardasil (Merck and Co., Inc.). Another HPV vaccine, Cervarix™ (GlaxoSmithKline Biologics), is in the process of obtaining FDA approval in the US.⁵ The antigen used in both HPV vaccines is the L1 major capsid protein of the virus that assembles into VLPs. The VLPs induce the production of neutralizing antibodies, therefore preventing pre-cancerous lesions such as cervical intraepithelial neoplasia (CIN). Gardasil is a quadrivalent vaccine that is effective against HPV types 6, 11, 16, and 18; Cervarix is a bivalent vaccine proved to be effective against types 16 and 18, and contains an additional immune-boosting adjuvant, AS04. The approved quadrivalent vaccine is administered in three intramuscular doses at zero, two, and six months. The bivalent vaccine is also given in a series of three doses, but at months zero, one, and six.⁵

Large phase III randomized, double-blind, placebo-controlled clinical trials have been conducted to demonstrate the efficacy of both vaccines. The FUTURE I study followed 5,455 women 16–24 years of age for three years after vaccination with the quadrivalent vaccine and found 100% efficacy in terms of prevention of anogenital lesions due to HPV types 6, 11, 16, and 18. The FUTURE II study assigned 12,167 women between 15 and 26 years of age to

receive placebo or the quadrivalent vaccine, and they were followed for three years. The primary end-point was CIN grade 2 or 3, adenocarcinoma *in situ* (AIS), or cervical cancer due to HPV types 16 or 18.⁵ With respect to the primary end-point, the vaccine was demonstrated to be 98% effective (95.9% confidence interval [CI] 86–100) in the per-protocol susceptible population and 44% (95% CI 26–58) in the intention-to-treat population.⁵ The overall vaccine efficacy against all high-grade cervical lesions regardless of HPV type was found to be 17% in the intention-to-treat population (95% CI 1–31).⁵ The quadrivalent HPV vaccine is highly effective in the prevention of HPV 6, 11, 16, and 18-related persistent infections, vaccine-type-related CIN, CIN 2/3, and external genital lesions such as genital warts, vulvar intraepithelial neoplasia (VIN), and vaginal intraepithelial neoplasia (VaIN).⁵

The international Papilloma Trial Against Cancer In Young Adults (PATRICIA) compared the bivalent vaccine and the hepatitis A vaccine (as control) in 18,664 women 15–24 years of age with an average follow-up period of 15 months.²⁰ The vaccine was found to be 100% effective in the prevention of high-grade lesions due to HPV types 16 and 18 (95% CI 74.2–100).²⁰ Both vaccines have demonstrated degrees of cross-protection to other HPV types ranging from 20 to 60%.⁵

The quadrivalent vaccine has been found to still be highly effective five years post-vaccination and the bivalent vaccine is still effective 4.5 years after vaccination.^{21,22} Studies are currently being conducted to fully assess the duration of efficacy of the two vaccines.

The effect of HPV vaccination on males is currently under investigation. One phase III observer-blind, parallel-group randomized study in Finland evaluated immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine (Cervarix) in males 10–years of age.²³ The subjects were randomized (2:1) to receive either the HPV-16/18 AS04 adjuvanted vaccine (n=181) or the hepatitis B virus (HBV) control vaccine (n=89) at zero, one, and six months and were followed for seven months. All initially seronegative subjects who received the HPV vaccine seroconverted by the second month. The vaccine induced seroconversion and high antibody titers for both antigens in all of the adolescent male subjects. The seroconversion rates of these adolescent men were similar to previously reported seroconversion rates in adolescent women.²³ The study reported that Cervarix is generally safe and well-tolerated and induces great immunogenicity in boys 10–18 years of age.²³ However, further HPV vaccination studies must be conducted in men to confirm this conclusion.

Adverse Events

The most common local adverse event reported on the quadrivalent vaccine was pain at the injection site. The most common systemic adverse event reported on the vaccine was pyrexia, which occurred in fewer than 5% of the vaccine recipients. Serious adverse events with the quadrivalent vaccine occurred in fewer than 1% and were similar in both proportion and type to those seen in the placebo group. There were no statistically significant reports of new diseases (such as autoimmune disorders) between the vaccine and placebo groups.

Cost-effectiveness of Vaccination

The estimated economic burden of the prevention and treatment of anogenital warts and cervical HPV-related diseases is over \$4 billion annually in the US in direct costs (this excludes other HPV-related diseases such as vaginal and anal

cancer).²⁴⁻²⁶ Of the \$4 billion in direct costs, \$200 million is due to the management of genital warts, between \$300 and \$400 million to the management of invasive cervical cancer, and the remainder, \$3.4-3.5 billion, to routine cervical cancer screening, follow-up on abnormal Pap smears, and pre-invasive cervical cancer.^{25,26}

Although it is much too early to assess the true impact of the HPV vaccine, various models have been developed to predict the impact of HPV vaccination. Vaccination of females 12 years of age could reduce the lifetime risk of cervical cancer by 20-66% depending on the efficacy and duration of the vaccine.^{27,28} Furthermore, Pap smear abnormalities could decrease by over 20%.²⁷ One model predicted that vaccination could reduce the lifetime risk for HPV-16-associated cervical cancer by up to 70%. The same model predicted that concomitant vaccination of male adolescents could prevent up to an additional 20% of cases of cervical cancer.²⁹

Several studies have hypothesized the cost-effectiveness of HPV vaccination with respect to cervical cancer screening. The estimated cost per quality-adjusted life-year (QALY) varies significantly between studies depending on the economic model used and factors such as the estimated duration of protection of the vaccine, frequency of cervical cancer screening, and vaccine coverage. The estimated cost per QALY gained by routine vaccination of females at 12 years of age varies from \$3,000 to \$24,300.^{27,28,30-33} If we assume life-long immunity from HPV vaccination, the cost-effectiveness ratio of vaccination of 12-year-old females was measured by one study to be \$43,00 per QALY gained compared with the current screening practice.³⁴

Recommendations

The recent approval for the public use of the quadrivalent vaccine in the US is a great opportunity to create a positive impact on the health of all individuals. The quadrivalent HPV vaccine is licensed for use in females nine to 26 years of age, which is the population in which the vaccine was found to be both safe and immunogenic. Due to the fact that HPV is sexually transmitted and is frequently attained soon after the onset of sexual activity, the Centers for Disease Control and Prevention (CDC) recommends vaccination for all females 11-12 years of age.⁵ Females can start the vaccination series as early as nine years of age.⁵ The CDC also recommends catch-up vaccination for females 13-26 years of age who have not yet been vaccinated. Although sexually active females in this age group may already have been infected with one or more of the HPV vaccine types, the majority will not have been infected with all four HPV vaccine types and would therefore still have some benefit from the vaccine. There is also the fact that the vaccine provides some degree of cross-protection to non-vaccine HPV types. Likewise, females with a history of genital warts may still benefit from the vaccine, and the vaccine is recommended in this subpopulation.

Due to the non-infectious nature of the vaccine, it can be administered in immunocompromised females. The HPV vaccine has also been proved to be safe in lactating women. Although it has been proved to be safe and is grouped as category B for pregnant women, it is still not recommended by the CDC in pregnant females; however, no intervention is needed if it is inadvertently given. Since the L1 protein for the formation of the VLPs is formed in *Saccharomyces cerevisiae* (baker's yeast) through the use of recombinant DNA technology, the vaccine is contraindicated in those with a history of allergy to baker's yeast. Pap tests and cervical cancer screening recommendations have not changed and vaccinated females are recommended to still undergo cervical cancer screenings as previously, since they may potentially become infected with a carcinogenic HPV type that is not covered by the vaccine.

Conclusion

Although the full effect of the HPV vaccines will not be evident in the near future, the potential impact on the lives of women is immense. The vaccine should be recommended and made available to all populations, especially in socioeconomic groups that have a low rate of cervical cancer screening. The quadrivalent HPV vaccine is recommended for females 11-12 years of age, but it is not mandated. There is great potential to significantly decrease the incidence of cervical cancer as well as other anogenital neoplasias and genital warts in the public. There is also the potential of significantly decreasing the economic burden of HPV-caused diseases, in addition to reducing intangible factors such as anxiety.

Future Directions

The approval of the bivalent HPV vaccine is pending in the US, but it is approved in Australia and Europe. Due to the nature of sexual transmission of genital HPV, there is much controversy around vaccination. Debate is still ongoing as to whether vaccination for HPV should be mandatory. The general public health benefit of HPV vaccination of adolescent males requires further investigation. Studies are needed to assess the efficacy of the vaccine in males in the prevention of anogenital neoplasias and genital warts and transmission of the virus to sexual partners. The direct health benefit of a male HPV vaccine would be mainly for the prevention of anogenital warts, as well as the possible impact on male fertility. However, HPV infection is common in males and is highly transmissible. Therefore, vaccination of males could significantly decrease disease rates in both males and females, as well as potentially influencing fertility rates. Optimal prevention measures must take into account the target age of adolescents and the possible benefits of vaccinating both adolescent men and women versus women only. If proper public health initiatives are put in place and prove to be successful in the vaccination of females of all socioeconomic classes, further evaluation and adjustments will likely be required for future guidelines on cervical cancer screening. ■

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