Getting to Know Human Papillomavirus (HPV) and the HPV Vaccines

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More than 100 types of human papillomavirus (HPV), of which more than 40 are transmitted sexually, affect men and women. The worldwide prevalence of cervical HPV infection is approximately 10%. The most common HPV types worldwide are 16 and 18, which are the main causative viruses for cervical cancer and are both preventable by vaccination. Two HPV vaccines are currently approved in the United States: the quadrivalent HPV recombinant vaccine in males and females and the bivalent HPV recombinant vaccine in females. The Advisory Committee on Immunization Practices does not recommend routine use of the quadrivalent vaccine in males. The vaccines have been demonstrated to be highly effective in preventing cervical dysplasia, vulvar cancer, and genital warts related to HPV types 6, 11, 16, and 18; they are most effective, however, in vaccinees who have never been infected with HPV. Based on a review of the literature, the authors argue that it may be appropriate to routinely vaccinate both males and females to prevent the spread of HPV types 6, 11, 16, and 18.

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years, with those having persistent infection being at the highest rate for the development of high-grade precancerous lesions or invasive cervical cancer.9

It has been estimated that at least half of sexually active males and females will acquire a genital tract HPV infection during their lifetimes,10 and many of them will acquire one during adolescence.11 Genital HPV infection is common in young sexually active females within the United States, as indicated by the following:

- The National Health and Nutrition Examination Survey assessed the prevalence of HPV infection in the United States by testing vaginal swab samples for HPV DNA in 1921 women. The prevalence was 27% overall and was highest (45%) among women aged 20 to 24 years.12
- A prospective study evaluated 608 female university students.16 Long-term follow-up of a subset of 156 students with cervical HPV was detected in 64% using polymerase chain reaction (PCR)-based testing.13 Another study14 that collected cervical and vulvovaginal swabs demonstrated that the 1-year cumulative incidence of initial HPV infection in 244 female college students was 28.5% after reporting intercourse with their first male sexual partner. The percentage of infected women increased to 39.2% after 2 years and 49.1% after 3 years.14
- A prospective study evaluated 608 female college students at 6-month intervals for 3 years; the evaluations included testing of cervicovaginal lavage samples for HPV DNA. At entry, 26% of the students were HPV positive. Among those who were initially HPV negative, 43% acquired HPV during the 3-year follow-up.15 A similar rate of new disease acquisition (32% in 2 years) was noted in another study of 603 female university students.16 Long-term follow-up of a subset of 156 patients with HPV infection at baseline demonstrated persistence of the same HPV type in 4.8% during an average follow-up of 4 years, in association with pathologic changes.17
- In a review of more than 3800 women aged 18 to 40 years, the overall prevalence of cervical HPV infection was 39.2%. Increased prevalence of high-risk, low-risk, and uncharacterized HPV genotypes was found with an increased number of sex partners. Detection of high- and low-risk HPV genotypes declined with increasing age.18

Although review of the above data may show the general percentages of HPV infection, it must be noted that many young men and women can be colonized with multiple oncogenic organisms at the same time. Most HPV infections are usually transient and ultimately clear; however, there still may be cytologic changes involved within the epithelium or mucosa of either sex.

One example of a transient HPV infection is that of anal HPV infections. Although study findings suggest that incident anal HPV infections are quite common, they tend to resolve fairly rapidly. One study of 431 sexually active women showed that 215 (50%) had at least 1 incident of anal HPV infection and that 58% of those with infections had documented viral clearance during a 15-month follow-up period; 87% of the cleared infections cleared within 12 months.19

Use of the HPV Quadrivalent Recombinant Vaccine

Currently, the HPV quadrivalent (HPV4) recombinant vaccine is approved for the prevention of HPV types 6, 11, 16, and 18; the targeted types are gender dependent. The vaccine requires 3 doses, with the second and third doses at 1 to 2 months and then 6 months, respectively, after the first. The HPV4 vaccine is approved for use in boys, girls, men, and women between the ages of 9 and 26 years. In females it is licensed to prevent outcomes related to HPV types 6, 11, 16, and 18; for men it is licensed to prevent genital warts caused by HPV types 6 and 11.20 A second type of vaccine, the HPV bivalent (HPV2) recombinant vaccine, is approved by the US Food and Drug Administration (FDA) for females aged 10 to 25 years to prevent HPV types 16 and 18.21

Vaccination is currently recommended for all girls and women aged 9 to 26 years whether or not they have ever tested positive for any HPV infection. The HPV4 vaccine is beneficial for at least 5 years, and studies are being done to determine overall long-term efficacy. Because the HPV4 vaccine is protective against 4 HPV types, it is important for women to be vaccinated even if they knew they were previously infected with 1 or more of the genotypes included in the vaccine. The HPV4 vaccine will not provide protection for HPV types that the vaccinated female already has. One contraindication to the HPV4 vaccine is pregnancy. Any woman who is pregnant should not have the vaccine until after her pregnancy is complete. Additional contraindications include those who previously had an allergic reaction to the HPV4 vaccine and those who have had "a severe allergic reaction to yeast, amorphous aluminum hydroxysphosphate sulfate, polysorbate 80."22

Results from vaccine studies for the HPV4 and HPV2 vaccines have shown that both vaccines are highly effective. In a study of 5455 women, in which 2723 women received the Gardasil vaccine, 98% of the women who were given the vaccine were protected against precancers (cervical intraepithelial neoplasia [CIN] 2 or 3, adenocarcinoma) caused by HPV for at least 3 years. One case of CIN was seen in the vaccinated group while 42 cases of CIN occurred in the placebo group.23 All 214 women who were given the HPV4 vaccine were protected against the external genital warts caused by HPV types 6 and 11 for at least 3 years. Six of 233 (2.6%) women developed precancerous cervical dysplasia or genital warts in the placebo group.24 In a study of 18,644 women aged 15 to 25 years, in which 9258 received the HPV2 vaccine and 9267 were given the hepatitis A vaccine, vaccine efficacy against cervical intraepithelial neoplasia was found to be 90.4%.25

HPV Infection in Males

Most sexually active people in the United States will have HPV at some point in their lives.26 Among men, prevalence estimates range up to 73%.5 There are more than 100 types of HPV, of which more than 40 are transmitted sexually, affecting men as well as women.27 The
Centers for Disease Control and Prevention (CDC) estimated that approximately 1% of sexually active men and women in the United States have genital warts at any given time.\textsuperscript{10} Penile cancer itself is rare, accounting for less than 1% of all men’s malignant tumors in developed countries.\textsuperscript{28} From 1973 to 2002, the overall incidence of primary, malignant penile cancer was found to be .69 per 100,000 males.\textsuperscript{29} Anal cancer is estimated to be diagnosed in 1.6 per 100,000 men and women per year.\textsuperscript{30} The CDC estimated that HPV-related penile cancer and anal cancer would be diagnosed in about 800 men and 1100 men, respectively, in the United States in any given year.\textsuperscript{10} An estimated 36% of penile cancers and 93% of anal cancers are due to oncogenic HPV types, primarily 16 and 18.\textsuperscript{4}

Some men are more susceptible to HPV-related diseases than others. For example, gay and bisexual men are 17 times more likely to develop anal cancer than heterosexual men. Also, men with weak immune systems, such as those infected with human immunodeficiency virus, are more likely than other men to develop anal cancer or severe cases of genital warts that are hard to treat.\textsuperscript{26}

Men are infected with HPV as it is passed through the genital tract. Most men and women have no pain or other indication of infectivity, aside from genital warts, so they may acquire HPV and pass the virus to their sexual partners without any knowledge of being infected. Individuals can carry the virus for many years after becoming infected.\textsuperscript{10} Because most men and women infected with HPV have minimal symptoms (typically none), it can be difficult to persuade men to be vaccinated against HPV.

Another consideration regarding routine vaccinations of boys and men is the cost-benefit analysis of the vaccine for men and the cost savings, in healthcare dollars, in women. According to the CDC’s National Immunization Survey, approximately 9.9% of women aged 18 to 26 years had ever received at least 1 dose of an HPV vaccine in 2007.\textsuperscript{31} Approximately 44.3% of adolescents aged 13 to 17 years had received at least 1 dose of an HPV vaccine, and 26.7% had received 3 doses.\textsuperscript{32} Now there is increased attention in achieving a similar vaccination rate in young women. The HPV4 vaccine has been shown to have 90% efficacy in preventing external genital lesions caused by HPV types 6, 11, 16, and 18 in males aged 16 to 26 years, similar to that reported for the same serotypes in females.\textsuperscript{33,34} Based on these data, the FDA considered the HPV4 vaccine for use in males. On October 16, 2009, the FDA approved use of HPV4 in males aged 9 to 26 years to prevent genital warts.\textsuperscript{20} In December 2010, the FDA approved the use of the HPV4 vaccine to also prevent anal cancer and associated precancerous lesions in both males and females aged 9 to 26 years.\textsuperscript{35,36} However, the Advisory Committee on Immunization Practices (ACIP) does not recommend routine use in men.\textsuperscript{20} The ACIP stated that the vaccine’s efficacy in preventing HPV-related cancers in men would be reviewed in future meetings.\textsuperscript{37} The ACIP recommendation is important because it serves as a guideline for primary care providers.

Given that HPV infection is the most common sexually transmitted disease within the United States, with more than 62 million new cases each year, reducing the overall incidence within the population should logically cause a correlating drop in overall transmission of the virus. As James Turner, MD, professor of internal medicine at the University of Virginia and chair of the Vaccine Preventable Disease Committee for the American College Health Association, remarks, “There is pretty good evidence that men are a reservoir of HPV and vectors for it. Protection makes sense, particularly if you can vaccinate boys before they become sexually active.”\textsuperscript{38}

**HPV Vaccine: Background**

Although the use of Papanicolaou (Pap) tests has reduced both the incidence and the associated mortality of cervical cancer by over 70%,\textsuperscript{39} many women still go untreated because they do not routinely undergo Pap test screening. An analysis of the CDC’s 1998 National Health Interview Survey of more than 100,000 individuals revealed that only 83% of women aged 40 to 64 years reported Pap testing in the previous 3 years.\textsuperscript{40} Screening rates are lower among women who are uninsured, younger, poorer, and less educated, probably contributing to the higher cervical cancer mortality in minority groups such as African Americans.\textsuperscript{41} Even among women who undergo screening, approximately 40% of those with abnormal Pap test results fail to return for additional testing.\textsuperscript{42,43}

These statistics show that although cervical cancer screening is effective in and of itself, too many individuals are still not receiving either preventive measures or treatment for this highly treatable disease. For this reason, the HPV4 vaccine has become another important means for physicians to help reduce the risk of cervical cancer and other diseases associated with the HPV virus. Several clinical studies have shown that the vaccine is efficient in protecting against infection by the 4 HPV types (6, 11, 16, and 18) associated with approximately 70% of all cervical cancer cases and more than 90% of all genital warts.\textsuperscript{1,3-44} It has the potential to reduce not only cervical cancer rates but also the rates of other diseases associated with the HPV virus, including anal and penile cancer.

In 1992, Kienbauer et al\textsuperscript{45} found that a major capsid protein of HPV could be expressed in cultured cells and self-assemble into viruslike particles (VLPs). These particular particles resembled HPV virions morphologically and were highly antigenic but did not contain oncogenic HPV DNA.\textsuperscript{46} Inspired by this research, a multivalent vaccine was developed that employed VLPs matched to the oncogenic HPV types to prevent genital warts and most cervical cancers.\textsuperscript{47} In 2006, there were at least 10 human randomized controlled clinical trials that had been conducted or were currently in progress to evaluate the 3-dose, HPV4 vaccine against HPV types 6, 11, 16, and 18. Outcomes for these trials examined the vaccine’s preventive efficacy for cervical and genital conditions, protection durability, immunogenicity, and tolerability and safety. Clinical endpoints were slightly different throughout the trials and consisted of persistent HPV infection, CIN, adenocarcinoma in situ, cervical cancer, external genital lesions or warts, vulvar intraepithelial neoplasia, vulvar cancer, and vaginal cancer.\textsuperscript{44,45}

The vaccine’s intended purpose is prevention and prophylaxis, and therefore efficacy is much greater in vaccinees
who have never been infected with HPV (ie, HPV-naïve patients) than in those who have had at least 1 previous serotypic infection. Although the vaccine proved to be at least 95% effective in preventing cervical lesions caused by HPV type 6, 11, 16, or 18 in females who were HPV naïve and received all 3 injections, it was only 36% effective in preventing such lesions in the general population.44 One can extrapolate from these data that the percentages would be similar in males, but no long-range studies are currently available to support this concept. In 2001, approximately 42.9% of girls in grades 9 through 12 in the United States reportedly have had intercourse,49 so that a relatively large proportion of girls (and, by extrapolation, boys) have already been exposed to HPV and would therefore not receive the full benefit of the vaccine series.

Another factor to be considered in evaluating the clinical effectiveness of this vaccine in both men and women is whether coinfection with multiple serotypes would enhance or diminish vaccine effectiveness. Vaccines may have in vivo cross-reactivity with serotypes already present in an individual. Two scenarios are possible. First, there may be a synergistic interaction whereby one serotype of the vaccine shares enough genetic qualities with another of the hundred or so possible serotypes that an immune response is mounted, preventing the spread of the close-linked serotypes.

Second, immunity is thought to be largely type specific, suggesting that most serotypes act competitively. If so, decreasing the prevalence of one serotype may trigger the process of “competitive release” and subsequent strains in the future. In summary, although the HPV4 vaccine has been demonstrated effective in preventing HPV infection in HPV-naïve females, it may not have the impact that marketers claim on cervical disease–related morbidity and mortality,54 nor are enough data available yet to ascertain how long it remains effective—an important consideration given that grade 3 CIN can progress to cervical cancer in 8 to 12 years.

Cost-Effectiveness Analysis

Cost-effectiveness analysis is a healthcare assessment that compares costs and outcomes for more than one healthcare alternative.54 Garber et al55 define it as a “method designed to assess the comparative impacts on expenditures on different health interventions.” After outliers were excluded, 6 studies showed a range of incremental cost-effectiveness ratios (ICERs) for the HPV vaccine between $16,600 and $27,231, with a median of $25,400. These ICERs include only the benefit from preventing HPV genotypes 16 and 18.56

The median ICER for HPV vaccination is high relative to those for other vaccination programs targeting the same population, such as the hepatitis B vaccination program. For countries of intermediate endemcity, the ICER for hepatitis B vaccination of infants and adolescents ranges between $251 and $1230 after conversion into 2006 US dollars.56 In one study, HPV vaccination in males was accounted for and resulted in higher ICERs (> $120,000) than in studies including only females.57

Many variables are associated with these cost studies, including but not limited to cross-immunity among HPV genotypes caused by mutation, “charge bias” caused by differences in vaccines and administrative costs, and preventive follow-up with Pap tests. The ICERs for a vaccination program may be high owing to false-positive outcomes of Pap tests. False-positive rates of 1% to 9% in large populations (from specificities of 91%-99%) lead to many unnecessary interventions in women with false-positive results. The effectiveness of vaccination programs also reflects differences in screening coverage rates among countries. Higher screening rates will decrease the benefits of vaccination, because these arise from additional cancer prevention beyond what can be accomplished by screening; with higher screening costs, ICERs will also be higher. Vaccination cost analyses must also account for differing healthcare costs among countries. HPV vaccination would probably be more beneficial in countries, such as the United States, that have a higher per capita expenditure for healthcare; such expenditure reflects many factors, including an upper-end gross national product base.56

Conclusion

Higher ICERs are only one factor to consider when determining whether or not to adopt a national or international vaccination program. Based on a review of the literature, it seems necessary to vaccinate both males and females to prevent the spread of HPV types 6, 11, 16, and 18.

There are still many unanswered questions regarding mandatory HPV vaccination. However, because HPV-16 and HPV-18 can be transmitted from males to females, a vaccination program in males should ultimately reduce transmissions to females. If the goal is mass immunization against a sexually transmitted disease process in one sex, it does seem logical to immunize the other sex as well. The quadrivalent HPV vaccine also protects men against genital warts caused by HPV types 6 and 11 and anal and penile cancer caused by types 16 and 18; here again, however, the cost-benefit ratio must be considered.

References


4. Reiter PL, Brewer NT, McRee A-L, Gilbert P, Smith


