Human Papillomavirus Vaccination

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Human papillomavirus (HPV) is a prevalent sexually transmitted virus, approximately 23 types of which can cause multiple cancers. Cervical cancer which claims about 4,000 lives in the U.S. yearly has recently been surpassed by oropharyngeal cancers as the most commonly occurring HPV-induced malignancy. The only available HPV vaccine in the U.S., Gardasil 9®, has the potential of preventing at least 90% of HPV-induced cancers, yet the possibility of an association between the vaccine and ovarian dysfunction still needs to be ruled out. In addition to utilizing HPV vaccine, healthcare providers should strive to promote sexual fidelity which could prevent not only HPV problems but other sexually transmitted infections and unwanted pregnancies.

Disease and Vaccine Background

Human papillomavirus (HPV) is the most common cause of new sexually transmitted infections (STIs) in the U.S.[1] HPV causes common warts, genital warts, and laryngeal papillomas,[2] as well as multiple cancers, including those involving the uterine cervix, mouth and throat (oropharyngeal), anal, and external genitals.[3] About 35 of the over 120 strains or types are mucosal/genital types generally spread sexually, at least 18 of which can cause cancer.[3] In recent decades, as increasing numbers of adolescents and adults have engaged in oral sex with multiple partners, oropharyngeal cancer caused by HPV has also increased.[4] It has in fact recently overtaken cervical cancer as the most common form of cancer caused by HPV.[5] The American Cancer Society estimates that 2018 will see over 51,000 new cases of oropharyngeal cancer with about 10,000 deaths, and over 13,000 new cases of cervical cancer with about 4,000 deaths in the United States.[6] Those numbers are not HPV specific since HPV DNA was found in 70% or less of the tested oropharyngeal, vulvar and penile cancers in the U.S.[5] Without Papinicolaou (Pap) smear (combined more recently with HPV DNA testing) screening, there would be many more cases of cervical dysplasia that would progress to deadly invasive cancer.[7] Cervical cancer requires a chronic (HPV infection that manifests as cervical intraepithelial neoplasia (CIN) years prior to developing into cervical cancer.[8] There are nearly 2.8 million abnormal Pap smears per year in the U.S.[9] Treatment for CIN and cervical cancer is costly and burdensome, and many women, especially in other countries around the world, do not get the needed screening for cancer prevention, resulting in much higher cervical cancer rates than in the U.S. and other developed countries.[10,11]

The first vaccine against HPV, Gardasil® (HPV4), was introduced in 2006 for females and in 2009 for males.[10] It contains immunity-inducing parts of four HPV types; 6, 11, 16 and 18. Types 6 and 11 cause at least 90% of anogenital warts.[12] Type 16 has been detected in over 90% of HPV-positive oropharyngeal cancers,[4] and is responsible for 54.5% of all cervical cancers, while type 18 accounts for 16.5% of cervical cancers.[3] Exposure to any of those four types as determined by seroprevalence (proportion of individuals with significant antibody levels) was as high as 42% in women aged 30 to 39 years and up to 18% in men aged 50-59 years based on a large U.S. study involving over 4,000 subjects in 2003-2004.[12] Antibody levels were not found to fall with increasing age, but women older than 38 in England had lower seroprevalence to types 16 and 18, presumably reflecting a change in sexual behavior in recent decades.[13] Exposure rates are significantly higher than seroprevalence rates because males more than females, frequently do not make detectable antibodies when infected. Infection rates are influenced by number of sexual partners. For type 16, seroprevalence ranges from 5% in the general male population,[12] to 12% in a population of sexually active males in Tucson, Arizona and Tampa, Florida,[14] and up to 48% in sexually transmitted disease clinics.[15] The 48% seroprevalence was found in those who tested HIV negative at a clinic testing men who had sex with men for HPV types 6, 11 and 16. A large (over 2,000 women ages 14 to 59) U.S. study[16] looking at prevalence of infection by polymerase chain reaction (PCR) testing found type 16 in 1.5%, type 18 in 0.8%, and any of the HPV4 types in 3.4% of

participants. Overall "HPV prevalence" (looking for 27 to 37 strains, 20 of which were considered low-risk types) was 26.8%. That prevalence varied by age; 24.5% for ages 14-19 years, **44.8% in 20-24 year-olds**, 27.4% in 25-29 year-olds, 27.5% in 30-39 year-olds, 25.2% in 40-49 year-olds, and 19.6% in 50-59 year-olds.

Another vaccine, *Cervarix*™ (HPV2), was released in the U.S. in 2009 [10] but is no longer available in the US. It contained only strains 16 and 18 , which cause most HPV-related cancers.[17] At the end of 2014, the FDA approved a 9-strain (HPV9) vaccine, Gardasil-9®, which includes strains 6, 11, 16, 18, 31, 33, 45, 52, and 58. The last 5 strains added to HPV9 are high-risk strains responsible for about 15% of cervical cancers,[18] but HPV9 may protect against about 90% of potential cervical cancer [19] not only by direct strain protection, but also by cross-protection between strains.[20]

Effectiveness

Both original HPV vaccines (HPV4 and HPV2) have made a significant impact on sexually spread HPV. Protection against complications like cervical dysplasia has been demonstrated, but is very limited if infection is acquired prior to vaccination.[8] Of interest, a new experimental vaccine is being tested that is showing some promise in reversing some HPV-induced cervical neoplasia.[21] HPV2 showed protection against both oral and cervical infections with HPV types 16 and 18 over a four year follow-up in Costa Rica.[22] In a 14-16 year-old sexually active Dutch population, HPV2 has also had excellent protection against new and prolonged (at least 6 months) infections with types 16 and 18, and there was some protection against infection with other strains.[23] With 4.5 to 10 years follow-up of 4,808 Finnish teenage women, HPV2 recipients had significantly fewer cases of grade 3 CIN (3 versus 75) than unvaccinated controls, and all 3 of the vaccinated CIN cases had type 16 DNA present before being vaccinated.[24] HPV4 use in Denmark has been associated with a significant decrease in cervical atypia and CIN in 18-20 year olds but not in older women (as expected since they did not have the benefit of the vaccine).[25] HPV4 use in the U.S. significantly reduced vaccine-type HPV prevalence between 2003 and 2012.[26] Effectiveness of at least 90% against HPV-related CIN with types 16 and 18 was found in the 12 years following HPV4 usage in Nordic countries, suggesting no need for booster doses.[27] HPV9 has likewise shown high (96.6%) efficacy against high-grade genital lesions and a 96.0% reduction in persistent infections associated with the 5 added strains in vaccinated girls.[19] Despite high expectancy of effectiveness, HPV vaccines are not 100% effective and follow-up exams and Pap smears will still be recommended, although the recommended frequency of Pap smears may be decreased.[19]

Longer follow-up studies may be more revealing regarding long-term protection for children who are vaccinated a decade or more before the onset of sexual activity, but antibody titers sustained up to 9 years after HPV2 administration indicate that long-term protection is likely for that vaccine.[28] Antibody levels after complete HPV9 series were significantly higher in recipients aged 9 through 15 years compared with females aged 16 through 26 years.[18] This observation, in addition to the limited effectiveness of the vaccine after HPV exposure, supports vaccinating at a younger age. Currently only 2 doses ofHPV9 are recommended for patients under 15 years of age versus 3 doses for 15 to 45 year olds.[29] Serology studies looking at protection after receiving multiple simultaneous vaccines such as Menactra® and Tdap along with HPV9 have found no detectable interference among the different vaccines.[18]

Safety

There were extensive safety trials before licensure of HPV4, HPV2 and HPV9. No significant concerns were found then or even in post-licensure studies.[30] With a higher rate of local reactions and syncope after HPV4 and HPV9, monitoring while sitting or lying for about 15 minutes after injection is recommended.[30] Local reaction rates were about 10% higher in HPV9 than in HPV4 female (but not male) recipients.[18] Potential adverse events including adverse pregnancy outcomes, autoimmune conditions,

demyelinating and other neurological conditions, thromboembolic problems, and stroke have been studied.[30-33] Post-vaccine rates have not been found to be different from background rates. The use of HPV vaccines in girls and women with special problems such as human immunodeficiency virus infections and systemic lupus erythematosus has also (with more limited study numbers – 319, 126, 100, 27) been found to be safe and effective.[30] In a large (N=997,585) Scandinavian study,[32] only three of 23 autoimmune events had significant association with HPV vaccination; Behcet's syndrome, Raynauld's disease, and type 1 diabetes. On further assessment, those three conditions had weak associations not temporally related to vaccine exposure. There was no association between venous thromboembolism and vaccine exposure and there were inverse associations with epilepsy.

The debate as to whether vaccinating adolescents against a STI such as HPV may contribute to an increase in premarital sex is not settled despite at least 5 studies purporting no such effect. A large (N=208,111) study examining health claims from 41 large employers across the U.S. found that sexually transmitted infection rates were higher in the year following vaccination (6.8 per 1000) than that found in unvaccinated controls over the same year (4.2 per 1000), but there was not any significant difference in the increases from before to after vaccination.[34] The vaccinated group had higher rates before vaccination. The vaccinated group rate (per 1000) went from 4.3 to 6.8 (58% increase) while the unvaccinated group rate went from 2.8 to 4.2 (50% increase). The unvaccinated group rate one year later still was slightly lower than the beginning rate of the vaccinated group. Another study claimed no increase in sexual activity in 11-12 year-old girls vaccinated against HPV versus controls vaccinated with other vaccines in the absence of HPV vaccination.[35] Their incidence rates for chlamydia testing were 2.20 vs. 1.50, pregnancy testing 4.32 vs. 3.02, pregnancy diagnosis 0.17 vs. 0.10, and counseling on contraceptives (excluding those with dysmenorrhea or acne) 1.39 vs. 0.50 in the HPV vaccine group vs. the control group. The study authors found "slightly, but not significantly, increased contraceptive counseling among HPV vaccine-exposed girls." This difference, however, is nearly 3-fold. Furthermore, a study from the Netherlands noted a significantly ($p < 0.002$) greater increase over time in the number of 14-16 year old girls that ever had sex in the vaccinated versus unvaccinated groups.[23] A questionnaire-based study of 16-17 year old girls in England found statistically non-different increases in sexual activity between the time an HPV vaccine was offered and 6 months later for vaccinated versus unvaccinated girls, yet the brief time period after a single dose of vaccine would not be expected to show a difference in sexual activity.[36] A Canadian study claimed, "We present strong evidence that HPV vaccination does not have any significant effect on clinical indicators of sexual behavior among adolescent girls."[37] Their "evidence" was based on comparing rates of STIs and pregnancies in those who could not be vaccinated (the year before it was first offered) with those who could be vaccinated, leaving out the factor of choice to vaccinate. A Swiss study found similar Chlamydia infection rates in vaccinees as in non-vaccinated young women, but submission of specimens was significantly associated with "having sexual intercourse," and every variable "linked to undergoing sexual activity were associated with vaccine acceptance by univariable analysis."[38]

There are some studies that more convincingly find no evidence of increased sexual behavior in association with HPV vaccination. A Nordic study found sexual debut and number of sexual partners to be very similar in vaccinated subjects and unvaccinated age-matched controls.[39] A very recent Canadian study actually found decreased rates of ever-pregnant as well as first sexual intercourse before age 14 in populations of girls largely (about 2/3) vaccinated against HPV in grades 6 through 9 from 2003 to 2013.[40] They claimed this as "evidence against any association between HPV vaccination and risky sexual behaviours" while acknowledging that they "did not examine the direct relationship between individual HPV vaccination status and sexual behaviours" and that there have been decreasing risky sexual behaviors in Canada and in other countries over similar time periods independent of HPV vaccine usage. Patients who are already sexually active or thinking about being sexually active prior to marriage would rightly be more willing to be protected by HPV vaccination, which may explain why rates of sexual activity are usually higher in vaccinated groups at baseline. Regardless of whether or not receiving HPV vaccine affects sexual behavior, adolescent girls and boys need to be counseled regarding the real risks of pre- or extra-marital sex. In the

absence of that health-risk behavior, there would be no sexually transmitted infections or HPV-induced cancer. For other information about benefits of abstinence before marriage, see the statement by the American College of Pediatricians on Abstinence Education.

Vaccination against HPV is not recommended during pregnancy, although there is accumulating evidence that there is little if any risk.[41] In a passive surveillance study of women exposed to HPV4 during pregnancy, with 2,802 enrolled between 2006 and 2012, an analysis from the first two years after licensure of HPV4 did not support a causal role between that vaccine and birth defects or other adverse pregnancy outcomes.[30] Ongoing assessments continue.

The U.S. maintains a passive reporting system of possible adverse events associated with vaccines called the Vaccine Adverse Event Reporting System (VAERS). In a recent review of 25,176 such events in females who had received HPV4 between June 2006 and March 2014, "no previously reported or new medical conditions were identified as safety signals which would require further evaluation."[26] Even so, there have been recent peer-reviewed case reports describing 6 cases of premature ovarian failure following receipt of HPV4.[42,43] The College conducted a search of the VAERS WONDER database in 2015 and found 12 cases of premature ovarian failure/premature menopause plus 77 cases since 2005 of amenorrhea of at least 4 months duration. HPV4 was associated with 86 of those 89 cases, and HPV2 with the other 3. None of those cases were associated with any other single vaccine type. See the 2016 statement by the American College of Pediatricians, New Concerns about the Human Papillomavirus Vaccine. VAERS reports were again analyzed in a 2018 study.[44] Of 17 cases of reported premature ovarian failure, 15 were discounted due to "insufficient information", and only 2 had a "physician diagnosis," both of which were diagnosed within a month of vaccination. It is true that VAERS reports are frequently of poor quality, but three of the premature menopause VAERS reports reviewed by the College had 35 months of more duration between time of vaccine initiation and onset of amenorrhea, all had "high" follicle stimulating hormone levels (one measured at 108) and "low" estrogen or anti-Mullerian hormone levels. The authors of the 2018 study reported that they "…did not detect any safety concerns for these conditions or for other reproductive problems in females."[44] Unfortunately, they did not examine reports of amenorrhea, which have been disproportionately associated with HPV4.

Another study from 2017 examined fecundabiity (ability to get pregnant) with respect to HPV vaccination.[45] They actually found higher fecundability in vaccinated females with a history of STIs and no vaccination effect overall. A wide age range (21-45 years) was used (including older women not likely to have been even eligible for HPV vaccination), and women who had been trying to conceive for > 6 menstrual cycles at enrollment were excluded while those who had been previously pregnant were not excluded. Another study published in September 2018 using diagnostic code mining in a large California Health Maintenance Organization to study Primary Ovarian Insufficiency (POI) in relation to adolescent vaccination, did not find any significant elevated risk of POI after adolescent vaccine use (including HPV).[46] Limitations of that study include: 1) a large age range (11-34) used in an 8 year study period; 2) most of the vaccines studied are clustered around ages 11 and 16, excluding much of the study population; 3) case ascertainment relied on passive surveillance for a population frequently treated with hormonal contraceptives that hide POI symptoms; 4) physicians involved with that population generally have a low index of suspicion for diagnosing POI and may not have ordered all the tests indicated to confirm the diagnosis; and 5) time from amenorrhea onset to POI diagnosis had a median of 3 years with a range up to 16 years in the study. In June 2018 a study was published indicating a 26% lower rate of ever having been pregnant in 25-29 year old US women who had received the HPV vaccine (which one was not specified) compared to those who had not received HPV vaccine.[47] Although those findings may have been significantly influenced by unknown confounding variables such as desire to get pregnant and use of birth control, the magnitude of these findings warrant caution until they can be verified or disproved. Design differences may explain the seemingly conflicting results between these three studies. Until there is further clarification as to whether or not HPV vaccine

can induce ovarian dysfunction, healthcare professionals, parents, and potential vaccine recipients should be made aware of this potential problem.

Recommendations

Given the effectiveness of vaccines against HPV infection and its morbidities, the American College of Pediatricians favors offering HPV vaccination to all children and young adults even if they are committed to abstinence until marriage, while at the same time sharing with parents (and older patients) recent concerns regarding future fertility. Although abstinence outside of marriage is clearly the most effective way to prevent all types of STIs, potential risk circumstances beyond an individual's control can occur, including sexual assault and the infection of one's future spouse. Parents should closely monitor their children's activities while reinforcing both morally and medically sound values. If parents do not model sexual fidelity or fail to restrict their children's exposure to sexually explicit media, including pornography, then they can expect their children to be at high risk for STI acquisition, and such children should not wait to be vaccinated against HPV. Also, parents should consider that many adolescents will be involved in high-risk activities without their knowledge, and waiting until these activities are recognized by the parents may place the child at risk for acquiring HPV. Finally, the College maintains that use of HPV vaccines should not be mandated by regulatory authorities, but must remain a personal decision by parents and their children.

The College is opposed to any legislation which requires HPV vaccination for school attendance. Excluding children from school over refusal to vaccinate for a disease spread only by sexual intercourse is a serious, precedent-setting action that trespasses on the right of parents to make medical decisions for their children. In addition, mandating vaccination as early as 9 years of age places the medical provider in an ethical dilemma. The administration of the vaccine requires explanation to both the parent and the child/adolescent. Parents may have chosen not to introduce the subject of sexual activity to their preteen children due to their physical and emotional immaturity. Most 9-12 year old children are not sexually active, and many have not even entered puberty. Forcing a parent to abandon his/her better judgment in order to discuss this information with the child would be inappropriate and unnecessarily intrusive.

HPV vaccines are approved for use down to 9 years of age in both males and females. For greatest impact, individuals should be vaccinated before sexual exposure to the virus, yet timing of administration is complicated by the uncertainties of both exposure risks and sustained vaccination benefits.

In summary, as any parent desires to protect their children from potential harms, including cancer, the American College of Pediatricians recommends that parents use the availability of HPV vaccines to usher in a discussion on human sexuality in a way consistent with their culture and values at a time when they determine their child/adolescent is ready to receive that information.

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The American College of Pediatricians is a national medical association of licensed physicians and healthcare professionals who specialize in the care of infants, children, and adolescents. The mission of the College is to enable all children to reach their optimal, physical and emotional health and well-being.

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