Multivalent prophylactic human papillomavirus (HPV) vaccines currently in the late stages of clinical testing are safe, immunogenic, and efficacious; and phase 3 tests of a quadrivalent vaccine show that it is 100% effective at preventing HPV types 16 and 18—associated cervical intraepithelial neoplasia grades 2 and 3, adenocarcinoma in situ, and cervical cancer through 2 years of postvaccination follow-up. These vaccines promise to reduce the burden of HPV-related disease. Realizing the full benefit of these vaccines will require a vaccination program that addresses the needs and concerns of healthcare providers, parents, and young adolescent patients who will be involved in the vaccine decision-making process. Osteopathic physicians, by virtue of their dedication to holistic care, are in an optimal position to play a key role in facilitating acceptance of these vaccines among potential vaccinees and their parents and guardians.

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Multivalent prophylactic human papillomavirus (HPV) vaccines in late stages of clinical development have the potential to reduce the incidence of cervical cancer, cervical intraepithelial neoplasia (CIN) grades 2 and 3, low-grade squamous intraepithelial lesions (LSIL), genital warts, and recurrent respiratory papillomatosis, as well as reduce the need for colposcopy and other surgical procedures.

In addition, vaccination is expected to reduce the anxiety and psychosocial morbidity that result from cervical disease, abnormal Papanicolaou (Pap) test results, and genital warts, as well as the significant costs of HPV-associated medical care. To fulfill this potential, however, HPV vaccines should be administered before the initiation of sexual activity; hence, children and young adolescents will be the primary target population for vaccination.

Parents will play a critical role in acceptance of these vaccines. They may have concerns related to vaccines in general or specifically to the HPV vaccines. Many people are dubious about the safety of vaccination, whereas others may object on religious grounds. The cost of these vaccines and access to healthcare will also play a role. Many will not have heard about HPV, and still more will be unaware of its links to cervical cancer and genital warts.

Speculation and media reports suggest that the sexual nature of genital HPV transmission will be an obstacle to the development of an HPV vaccine program. Healthcare providers (eg, physicians, certified nurse midwives, nurse practitioners, physician assistants) must be prepared to discuss the risks associated with HPV infection and the benefits of HPV vaccination with their patients. Osteopathic physicians, with their holistic approach, are better positioned to provide anticipatory guidance to parents of children and young adolescents before sexual debut.

Addressing Safety Concerns

Many parents have concerns about the general safety of vaccines. Approximately 2% of participants in a quota sample of parents with children aged 0 to 6 years (n=1768) were not confident in the safety of childhood vaccination, whereas an additional 14.5% were only “somewhat” confident. These concerns are associated with both income and education level: individuals with incomes of $50,000 to $74,999 were more likely than both higher and lower income groups to say that they were “somewhat” or “not at all” convinced of the safety of childhood vaccination. High school graduates were also more likely to doubt the safety of childhood vaccinations than were individuals who had dropped out of high school, or who had received even some college education.

Individuals who lacked confidence in the safety of childhood immunizations were also less likely to endorse questionnaire measures such as “I usually follow my child’s doctor’s advice.”1 When speaking to these parents, it may be helpful for healthcare providers to emphasize the excellent safety record of the HPV vaccines, such as the fact that not a single serious vaccine-related adverse event has occurred in any trial of any HPV vaccine to date. Additionally,
the high likelihood that their children will be infected with HPV if they do not receive the vaccine should be reinforced: it is estimated that 70% of all sexually active individuals will be infected with HPV at least once in their lifetime.\textsuperscript{2,3}

**Cost of Vaccine and Access to Healthcare**

Both the cost of vaccine and the access to healthcare can mediate between theoretical acceptance and actual implementation of vaccination. It is not yet known what HPV vaccination will cost if the cost of vaccination is covered by insurance. Even if the cost of vaccination is covered by insurance, 11% of young adolescents (ages 10 to 14 years) have no insurance whatsoever.\textsuperscript{4} The cost of vaccine and the lack of access to healthcare are expected to be significant barriers for some individuals.

In addition, adolescents do not frequently visit a physician. Among high school–aged students (ages 15 to 18 years), 13.7% of whom have no health insurance,\textsuperscript{4} 39.6% of females and 42.5% of males had not had a visit to a healthcare provider for preventive care (eg, not related to illness or injury) in the past 12 months.\textsuperscript{5} Human papillomavirus vaccination will require three visits during a 7-month period, which may be a significant commitment in a population that does not frequently visit a healthcare professional. The hepatitis B virus (HBV) vaccine demonstrates how a vaccine series can be promoted effectively if positioned as a requirement for a school entry. Knowledge-based decisions and widespread support for the HBV vaccination have resulted in a high compliance rate and an increase in herd immunity.

**Lack of Knowledge About Human Papillomavirus**

Despite being at high risk for HPV infection, college-aged individuals do not know much about HPV. Yacobi et al\textsuperscript{a} surveyed college students (n=289; 63% female, 37% male) by a mailed self-administered questionnaire that assessed their knowledge of HPV and attitudes toward HPV.\textsuperscript{6} Of those sampled, 38% had never even heard of HPV, and the students knew significantly less about HPV (knowledge score on 3-point scale: 1.5; \(P=0.001\)) than they did about the human immunodeficiency virus (HIV) (2.6), chlamydia (1.9), gonorrhea (2.1), herpes (2.3), hepatitis B (2.1), or syphilis (2.1).

The participants in the survey by Yacobi et al\textsuperscript{a} also confused HPV with other sexually transmitted diseases (STDs); some patients thought HPV was the causative agent of herpes or the acquired immunodeficiency syndrome, whereas 22% confused genital warts with herpes. Approximately 59% did not know how HPV was transmitted; only 21% of the respondents believed that they were at risk for HPV infection; and 71% did not know that HPV could result in clinical complications such as cervical cancer.\textsuperscript{6}

A second, smaller study supports the finding that college students know little about HPV, and know less about HPV than they do about other, less common sexually transmitted infections (STIs). Lambert\textsuperscript{7} administered a questionnaire to 60 college students which included simple questions about HPV regarding its high prevalence and links to genital warts and cervical cancer, and questions about other STDs. Participants were significantly more likely to correctly answer questions about non–HPV-associated STIs (87% correct) than HPV (45% correct). Women did no better than men on the HPV-related questions, despite the fact that they bear a larger share of HPV-associated disease.\textsuperscript{7}

Ignorance about HPV is by no means limited to college students. A qualitative interview study of 20 adolescent females (ages 14 to 18 years) recruited in health clinic waiting rooms found confusion about Pap testing, HPV, and HPV-associated disease.\textsuperscript{8} Approximately 85% of the adolescents had undergone a Pap test, but only 35% were able to state the purpose of Pap testing; most thought that the purpose of a Pap test was to diagnose infection, assess childbearing status, or examine the reproductive organs. Although 45% of the adolescent respondents knew at least one person with cervical cancer, none named HPV infection as a risk factor for cervical cancer. Participants were somewhat more familiar with genital warts: 45% were able to describe the symptoms of genital warts, though some confused genital warts with herpes, and 40% of respondents were familiar with the persistent nature of genital warts.\textsuperscript{9}

It may be difficult to persuade young adults to seek vaccination against an STI of which they are unaware. Education about HPV, its prevalence, and the clinical complications associated with infection may help to pave the way for vaccination efforts. Thus, healthcare providers must be prepared to educate both patients and parents about the risks associated with HPV infection and the benefits of vaccination.

**Potential Vaccinees’ Attitudes Toward Vaccination**

To date, no studies have been conducted assessing acceptance of vaccination in the young, sexually naïve adolescents who would be the targets of HPV vaccination. Studies have been conducted, however, in adolescent and young adult women in their teens and 20s.

Boehner et al\textsuperscript{9} assessed factors affecting acceptance of HPV vaccine among college aged men (n=127) and women (n=129). The vaccine was presented as either a vaccine against genital warts or a vaccine against genital warts and genital and cervical cancer. Type of vaccine had no statistically significant effect on acceptance; overall, 74% of respondents were interested in receiving a vaccine for HPV. Factors predicting acceptance of HPV vaccine included having had a greater number of sexual partners, thinking that their parents would encourage vaccination, and low cost and safety of the vaccine.\textsuperscript{9}

Kahn et al\textsuperscript{10} assessed acceptability of HPV vaccination to prevent cervical cancer in adult women aged 18 to 30 years, as well as their acceptability of vaccinating their hypothetical 12-year-old daughters.\textsuperscript{10} Of the women surveyed, 89% endorsed HPV vaccination for themselves, and 81% endorsed it for their “daughters.” The following were associated with vaccine acceptance: knowledge about HPV (\(P=0.004\)); belief that getting the vaccine was a good idea (\(P=0.004\)); number of lifetime sexual partners (\(P=0.028\)); and belief that people such as healthcare providers (\(P=0.028\)), parents (\(P=0.015\)), a husband or steady sexual partner (\(P=0.016\), and “most people”
important to the individual \((P=.005)\) would support vaccination.\(^{10}\)

Both of these studies found that vaccine acceptance correlated with level of sexual activity. Unfortunately, although individuals with a greater number of sexual partners might be more accepting of HPV vaccination, it is likely that these people have already been infected with HPV. These studies also demonstrated that potential vaccinees are more accepting of vaccination when they think that individuals important to them, such as their parents, would support vaccination. This finding suggests that educating parents about HPV and HPV vaccination may be crucial to obtaining not just parents about HPV and HPV vaccination. This finding suggests that educating parents about HPV and HPV vaccination may be crucial to obtaining not just their consent, but also that of their children.

**Attitudes About Vaccine Among the Parents of Potential Vaccinees**

Qualitative interviews to assess parental acceptance of four hypothetical STI vaccines, offering protection against HIV, genital herpes, gonorrhea, and HPV, were conducted with 34 parents of children aged 8 to 17 years who were visiting either a clinic or private physician’s office.\(^{11}\) Approximately 73% of the parents indicated that they would vaccinate their children against HPV. The investigators queried the parents who had accepted all four vaccines to determine the motives behind their acceptance and found that these parents cited a wish to protect their children, concern about the diseases associated with an STI, and personal experience with the STI in question.

Parents who rejected one or more of the four vaccines perceived their children to be at low risk, often because the parent did not think the child was sexually active, or they were not concerned with the outcome of an STI. Some parents who refused vaccination said that if they thought their children had become sexually active, they would endorse vaccination.\(^{11}\)

A second qualitative study investigated parental response specifically to an HPV vaccine.\(^{12}\) Twenty-five parents, each with at least one child between the ages of 10 and 15 years, participated. Again, vaccine acceptance was correlated with perceived risk: parents who thought that their children were likely to be exposed to HPV at some time in their life were more likely to endorse HPV vaccination for their children.\(^{12}\) The interviewers also asked whether the parents thought boys should be vaccinated as well as girls even though the vaccine would have less benefit for boys. Most parents thought that boys should also be vaccinated to protect their sexual partners and reduce overall disease transmission.\(^{12}\)

The results of these qualitative studies suggest that when discussing the HPV vaccine with parents, the healthcare providers should make sure that the parents understand that all sexually active individuals are at high risk of acquiring HPV. It may also be helpful to cite the high prevalence of the disease, especially in younger populations, and the fact that infection is often acquired soon after sexual debut. These pieces of information may help underscore the importance of vaccinating before sexual debut.

DiClemente and Prochaska’s model of change\(^{13}\) (Figure 1) is a useful way of thinking about parents who may be ready to change their attitudes toward vaccination. Physicians can help move parents from the precontemplation phase into the contemplation phase by providing information about HPV and HPV vaccination, and conduct them through planning and eventually, action.

Popular media sources have speculated that some parents may object to HPV vaccination despite its clear cancer-prevention benefits, because they think that HPV vaccination would encourage unsafe sexual practices or that HPV vaccination would be perceived as condoning sexual activity. Physicians should address such concerns at the appropriate opportunity, being aware:

- The three visits required for HPV vaccination may prove a useful occasion to discuss sexual health and behaviors with both the patient and the patient’s parents.
- Parents may feel more comfortable with vaccination if they know it is being given in the context of strong messages about sexual health and well-being.

**Vaccine Preferences**

A few studies have investigated the role of the vaccine’s properties, such as cost, efficacy, and disease(s) targeted, in vaccine acceptance. Forty adolescent (ages 14 to 18 years) and adult (ages 20 to 50 years) females were asked to evaluate the acceptability of nine HPV vaccines that varied in terms of cost, efficacy, whether they protected against cervical cancer or both cervical cancer and genital warts, and whether a physician specifi-
cally recommended the vaccine. Both the adolescents and adults showed preference for the same vaccines: those with higher efficacy (90%), specific physician recommendation, and low or moderate cost. Whether the vaccine provided protection against genital warts in addition to protection against cervical cancer did not figure largely in decision making.

A second study, however, found that all other things being equal, disease(s) targeted by HPV vaccines did play a role in vaccine acceptance. A convenience sample of 60 females aged 15 to 28 years were surveyed about HPV knowledge, attitudes toward HPV vaccination, and potential willingness to participate in a clinical trial of an HPV vaccine. Given a choice between a hypothetical vaccine that protected against 85% of cervical cancers and no protection against genital warts and a vaccine that offered protection against 70% of cervical cancers and 100% of genital warts, 83.3% (P<.001) of the sample chose the vaccine that offered protection against both cervical cancer and genital warts (Figure 2).

Attitudes of Physicians

Approximately 1200 fellows of the American College of Obstetricians and Gynecologists (ACOG) were asked to rate their willingness to recommend HPV vaccination in 13 different scenarios that differed in age of vaccinees (13, 17, or 22 years), vaccine efficacy (50% or 80%), diseases targeted (cervical cancer, genital warts, or both), and whether the ACOG had recommended the vaccine. Hoover et al collected and assessed 181 surveys. The average acceptance score for all scenarios was 79 (100 was “definitely recommend”). Participants preferred vaccines that protected against cervical cancer or both cervical cancer and genital warts, were recommended by ACOG, and were efficacious, and they preferred to vaccinate older (17- or 22-year-old) individuals.

A second study investigated the attitudes of nurse practitioners (n=224) toward vaccinating adolescent patients against STIs. Based on the presentation of 13 vaccination scenarios that varied by age (11, 14, or 17 years) and gender of the patient, diseases targeted (HIV, genital herpes, or mononucleosis), and whether the American Academy of Pediatrics had endorsed the vaccine, the nurse practitioners were asked to rate their willingness to recommend the vaccine. Like the ACOG fellows, the nurse practitioners preferred to vaccinate older rather than younger patients. They also strongly preferred vaccines that a professional body had recommended. They did not show a preference for vaccinating males or females, but unlike high-risk HPV infection, the diseases mentioned in this study had equally negative effects for men and women. Nurse practitioners who spent at least 25% of their time working with adolescents were more likely to recommend vaccination than were nurse practitioners who spent less than a quarter of their time working with adolescents (P<.02).

Figure 2. Preferences of females aged 15 to 28 for a vaccine that protects against 70% of cervical cancer and 100% of genital warts as opposed to 85% of cervical cancer. (Source: Hoover DR, et al. Attitudes of adolescent young adult women toward human papillomavirus vaccination and clinical trials. Health Care Women Int. 2000;21:375–391.)

In addition, an informal survey of 837 osteopathic physicians attending an American Osteopathic Association-sponsored symposium on HPV in October 2005 found that more than 90% of these physicians would promote a vaccine that would reduce or prevent HPV infection.

Two themes emerge from these surveys: first, recommendation by a professional organization is key to physicians’ use of vaccine; and second, physicians may be uncomfortable vaccinating young adolescents against STIs. For maximum efficacy, however, these vaccines must be administered to sexually naive individuals. The median age at which sexual activity is initiated in the United States is 16, so vaccinating at age 17, 22, or even 14 years will be too late for many adolescents.

Professional organizations are influential in the vaccination choices of physicians and can facilitate vaccination of younger adolescents by including an age in any recommendations that they make about HPV vaccination.

Comment

Multivalent HPV vaccines promise to reduce the incidence of cervical cancer, cervical dysplasia, and genital warts, as well as reduce the psychosocial morbidity associated with these diagnoses and abnormal Pap test results. For maximum efficacy, however, these vaccines must be administered to sexually naive individuals. The low age of sexual debut and high prevalence of HPV among sexually active youth make vaccination in early adolescence before the sexual debut the preferred option. Vaccinating these young adolescents, however, requires incorporating their parents’ consent in the decision-making process. Healthcare
providers will need to overcome their preference to vaccinate older patients. Although surveys indicate that most parents are interested in vaccinating their children against HPV, those who are not are generally uninterested because they do not perceive HPV as a threat to their children. It is necessary to inform such parents that HPV is a threat to all sexually active individuals. Parents who are concerned about condoning sexual activity or unsafe sex should be encouraged to think of vaccination as an opportunity not just to prevent cervical cancer, but also to discuss these issues with their children. Osteopathic physicians will have a crucial role in facilitating acceptance of HPV vaccine, and thus they will enable the promise of multivalent HPV vaccines to be realized.

References