Despite strong evidence of efficacy, as well as vigorous public health efforts, rates of human papillomavirus (HPV) vaccination among adolescents remain low. The generally poor rate of vaccination is exacerbated by socioeconomic disparities.
The authors discuss the scope of the HPV vaccination problem, barriers to vaccine acceptance, and public health and individual provider measures that have potential to increase initiation and completion of the vaccine series. The authors conclude that if primary care providers and public health organizations put sufficient effort into immunization practices and vaccine education programs, improvements in HPV vaccination rates among adolescents can be expected—similar to improvements achieved with other vaccinations.

The Centers for Disease Control and Prevention (CDC) estimates that 50% of sexually active adults will become infected with human papillomavirus (HPV) during their lifetimes. Infection with HPV is the most common sexually transmitted infection among sexually active female adolescents, with a prevalence of 18.3% according to Forhan et al. Nearly 100% of cervical cancer cases are associated with HPV infection. As many as 25% of HPV-related cancers occur in men.

Two vaccines have been developed for the prevention of HPV infection, and both vaccines are offered as a 3-dose series that is typically completed over the course of 6 months. Gardasil (Merck & Co Inc, Whitehouse Station, NJ), the quadrivalent HPV vaccine, provides immunogenicity against HPV genotypes 6, 11, 16, and 18. Cervarix (GlaxoSmithKline Biologicals, Rixensart, Belgium), the bivalent HPV vaccine, provides coverage against HPV genotypes 16 and 18. The latter two genotypes are associated with the vast majority of cases of cervical cancer and advanced cervical intraepithelial neoplasia (CIN) worldwide. Genotypes 6 and 11 are associated with the majority of cases of condyloma acuminate (i.e., genital warts).

The burden of genital cancer is not borne solely by women. An estimated 7000 cases of cancer associated with HPV genotypes 16 and 18 (primarily anal, penile, and oropharyngeal cancers) occur in men annually in the United States. Children born to mothers with active condyloma acuminate at the time of delivery are at risk of respiratory papillomatosis—a disease that can lead to dysphonia, severe respiratory distress, and multiple surgical procedures during childhood.

Despite mounting evidence of the benefits of HPV vaccination, the numbers of eligible patients who begin or complete the vaccine series remain startlingly low. Data consistently demonstrate a need for increased education of patients, parents, and providers regarding the benefits of the HPV vaccines and common misconceptions about their use. In the present article, we address concerns regarding the HPV vaccines, and we discuss public health and individual provider efforts that have the potential to increase rates of HPV vaccination.

**Current immunization practices**

The CDC’s Advisory Committee on Immunization Practices (ACIP) began to recommend universal vaccination against HPV for girls and women in 2006. The ACIP recommends that all girls aged 11 to 12 years receive the HPV vaccine series, and that “catch-up” immunization be provided to females aged 13 to 26 years. If the patient’s social history indicates sexual precocity, the vaccine can be administered as early as age 9 years, at the provider’s discretion. Although this administration schedule is designed to promote vaccination before the onset of sexual activity, individuals who are already sexually active or infected with HPV should also receive the vaccine. The vaccine will provide protection against HPV strains that the sexually active adolescent may not have contracted, but it will not protect against current HPV infections in the adolescent.

Routine completion of the 3-dose HPV vaccine series is problematic. Survey results suggest that in 2009 only 44% of US girls aged 13 to 17 years had received 1 or more HPV vaccines, and only 27% of US girls had received 3 HPV vaccines. Although these percentages improved over the 2006-2009 study period, other studies have revealed similar results. In 2010, 48.7% of US girls aged 13 to 17 years received an HPV vaccine, and 32% completed the 3-dose series. These percentages reflect overall improvement, but substantial work continues to be necessary to achieve widespread completion of the entire HPV vaccine series.

Furthermore, apparent disparities exist in HPV vaccine coverage when race and
income are considered. Although rates of initiating the HPV vaccine series have not been associated with socioeconomic status, completion of the 3-dose series was found to be lower among patients living below the poverty level. African American and Hispanic women—populations known to have higher rates of cervical cancer—were less likely to complete the HPV vaccine series than were white women.\textsuperscript{13}

The quadrivalent and bivalent HPV vaccines are approximately 93% to 98% effective in reducing the occurrence of high-grade CIN caused by HPV genotypes 16 or 18 within 3 years of vaccination.\textsuperscript{9,14} Both HPV vaccines have also demonstrated cross-protection against the nonvaccine oncogenic serotypes (ie, HPV genotypes 31, 33, 45, 52, 58).\textsuperscript{15} In addition, both HPV vaccines are highly immunogenic in boys and men (ie, >99% immunogenicity in recipients of either the quadrivalent or bivalent vaccine), and vaccination with the quadrivalent vaccine demonstrates 90% efficacy in reducing external genital lesions related to HPV genotypes 6, 11, 16, and 18.\textsuperscript{16,17} Although studies in males are promising to date, they have lacked sufficient follow-up time, because penile intraepithelial neoplasia tends to develop later in life.

In October 2011, the ACIP recommended universal immunization of boys aged 11 to 12 years with 3 doses of the quadrivalent HPV vaccine.\textsuperscript{19} As with girls, providers can start immunizing boys at age 9 years if the boys are considered at high risk, and providers are advised to offer catch-up immunization for boys between ages 13 and 26 years.\textsuperscript{19}

The quadrivalent HPV vaccine appears to be well-tolerated, with the majority of adverse events being mild to moderate localized injection-site reactions.\textsuperscript{19} Postlicensure studies in females have revealed an increased likelihood of syncope on the day of vaccine administration.\textsuperscript{20} As a result of that finding, the ACIP advises that girls and woman be observed for 15 minutes in the office after HPV vaccine administration. Although no analogous studies have been performed in males, similar safety measures should be taken when boys and men receive HPV vaccination.

Barriers to compliance
In a survey of adolescent vaccination coverage, the most commonly reported reasons for not receiving vaccination against HPV were lack of knowledge about the vaccine, failure of the provider to recommend the vaccine, lack of school vaccine requirements, and no reported sexual activity in the adolescent patient.\textsuperscript{21} A meta-analysis of HPV vaccine acceptability among adolescents, young adults, and parents revealed that, across surveys, 42% of respondents were aware of HPV, and 21% of respondents knew that HPV infection was common.\textsuperscript{21} The knowledge that HPV can cause cervical cancer was generally low (ie, 44% across surveys), but this knowledge level varied greatly depending on the particular survey. In addition, surveys revealed that inaccurate perceptions of HPV vaccine safety continue to be major barriers to patient and parental acceptance of vaccine administration.\textsuperscript{21} Another study revealed that some physicians do not supply or offer HPV vaccination because of high cost and uncertainty of reimbursement.\textsuperscript{22}

As with most preventive health care interventions, efforts to increase completion of the HPV vaccine series involve patients and parents, health care providers, insurance providers, and local and national health care policy makers. Effective interventions should target patient, parent, and physician awareness and compliance with universal recommendations.

Public health strategies to improve compliance
Adolescents are less likely than younger children to seek preventive care and, as a result, are less likely to receive adequate and timely vaccination.\textsuperscript{23} Increased public health efforts designed to raise awareness of the primary care needs of adolescents may lead to an increase in the number of adolescent patients entering the primary care office. Coordinating those efforts with increasing education about HPV and HPV vaccination would further serve to solidify awareness among the adolescent population of the importance of routine primary care visits and immunoprophylaxis. Support for this type of awareness campaign can be found in a 2007 study that showed that mothers who were educated about HPV transmission and prophylaxis were more likely to have their children vaccinated against the virus.\textsuperscript{24}
Vaccination rates for varicella and hepatitis B approach 97%, largely because of school entry requirements.\textsuperscript{25} As of March 2012, 13 state legislatures had passed laws requiring funding or educating the public about HPV and HPV vaccination, and such legislation had been introduced in more than 25 other states.\textsuperscript{26} Currently, Texas, Virginia, and Washington, DC, require HPV vaccination for girls to enter the sixth grade.\textsuperscript{27} Enacting additional state-mandated HPV vaccine requirements would potentially improve vaccine coverage rates and have the secondary benefit of encouraging adolescents to access primary care services.\textsuperscript{27} Mandating HPV vaccination would also potentially add to the perceived importance of this prevention measure. Furthermore, public awareness measures in which HPV vaccination is compared with other adolescent vaccines, such as the meningococcal vaccine, may improve public acceptance. It is important that the normalcy of receiving HPV vaccination be emphasized. If the public perceives the HPV vaccine series as beneficial and routine, there is a greater likelihood of vaccine acceptance.

Access to HPV vaccination is an important factor that influences vaccination compliance, and public policies have been enacted to support more widespread access. Under the Affordable Care Act, insurance companies are required to cover all ACIP-recommended vaccines—including the HPV vaccine series—for anyone who enrolls in a new insurance plan after the September 23, 2010, signing of the law.\textsuperscript{28}

The Medicaid Vaccines For Children (VFC) program pays for vaccines for children aged 18 years or younger who are Medicaid-eligible, uninsured or underinsured, Native American, or Native Alaskan.\textsuperscript{29} States with State Children’s Health Insurance Programs (SCHIPs) that are separate from their Medicaid programs are federally required to use state funds to cover ACIP-recommended vaccines for children, because children in these programs are ineligible to receive coverage under VFC payments.\textsuperscript{29} Both Merck and GlaxoSmithKline offer assistance programs providing their HPV vaccines free of charge to women older than age 18 years who are uninsured or unable to pay for the vaccines.\textsuperscript{30,31}

Provider strategies to improve compliance

The factor most strongly associated with initiating the HPV vaccine series is provider recommendation.\textsuperscript{32} It is important for each physician to be a confident advocate for vaccination against HPV, including being prepared to respond to parental concerns regarding adverse effects of the vaccines. In addition, physicians should capitalize on office visits of adolescents for acute problems and sports-related physical examinations to review the adolescents’ immunization records and administer vaccines as appropriate.

Many parents refuse the HPV vaccine because they believe that their child is at low risk for sexual activity. This parental attitude may impact physician willingness to pursue vaccination at the ACIP’s recommended ages. Before the widespread availability of the HPV vaccine, a survey of 150 family physicians revealed that they were more likely to recommend the vaccine to older women than to female adolescents.\textsuperscript{33} As younger adolescents become older adolescents, they typically have fewer preventive medicine visits to physicians, and, thus, physicians have fewer opportunities to recommend vaccination. Moreover, parental and physician estimates of onset of sexual activity in adolescent patients can be inaccurate. Vaccinating children at age 11 years—when patients are more likely to comply with follow-up appointments and before the onset of sexual activity increases—the potential of completing the HPV vaccine series.

Some physicians do not offer HPV vaccination because of high cost. These physicians need to become aware of various programs designed to increase vaccine affordability and ensure reimbursement. This includes becoming a VFC provider through the CDC by contacting their state’s VFC coordinator.\textsuperscript{34} Alternatively, physicians can refer their patients to local public health or community health centers that provide vaccination at low cost or no cost. In addition, school-based health centers are an often overlooked resource for immunizations for patients in uninsured and low-income families.\textsuperscript{35}

Many parents express concerns about the potential effects of the HPV vaccine on their child’s sexual activity, including the possibility that vaccination will cause a false sense of security that will lead to increased promiscuity.\textsuperscript{36} A 2008 survey of physician attitudes regarding the HPV vaccine revealed that 11% of the responding physicians would not recommend the vaccine because of such concerns.\textsuperscript{36} However, as the
authors of that study contended, the best barrier to high-risk sexual practices is awareness and communication among providers, parents, and patients. Discussing HPV vaccination with parents and patients provides a good starting point for that communication. Furthermore, physicians can reinforce the importance of HPV vaccination outside of their practices, such as by submitting educational letters to the editor and opinion-editorial pieces to print and online news resources.

The problem of poor patient compliance with vaccine follow-up can be addressed by using reminder and recall systems, which have previously been shown to increase vaccination rates among adolescents. Studies suggest that reminder telephone calls, text messages, or e-mails can improve rates of completion of the HPV vaccine series. Indeed, a text-message reminder system has been shown to improve the on-time receipt of the second and third HPV vaccines. Text-message reminders are well accepted by parents. Commercial websites, like ohdontforget.com, can be used by providers or office staff to send text message reminders to patients. More advanced software, like Doctor Connect, can integrate with many current office management software programs to streamline the reminder scheduling process.

As with other childhood vaccines, if the interval between HPV doses is prolonged, there is no need to repeat doses or restart the HPV vaccine series. A study published in the Journal of the American Medical Association in April 2011 revealed that adolescent females who received the 3 HPV doses in 9- and 12-month schedules had minimal, clinically insignificant decreases in HPV antibody titers, compared to adolescent females using the standard 6-month schedule. These results support the idea that physicians should not be hesitant to proceed with the HPV vaccine series if a patient presents late for booster vaccinations.

**Future direction**

The finding that HPV vaccines have adequate efficacy despite delayed administration suggests that adequate immunogenicity can be achieved with fewer than the recommended 3 doses. Compared to the standard 3-dose HPV series, recent studies demonstrate similar immunogenicity when 2 HPV doses were administered 6 months apart to females in the target age range. A move toward a double-dose series—and potentially even a single dose—would have a clinically significant beneficial impact on rates of completion of HPV vaccination.

**Final notes**

By making adjustments to the way we practice, physicians can continue to improve public acceptance of, and compliance with, the HPV vaccine series. For physicians involved with public health efforts, continuing to provide focused education to target patient groups will contribute to the momentum of vaccine compliance. Every physician can play a role in public health by writing letters to local news outlets to inform the public about the importance of HPV vaccination. Physicians can also promote legislation that would mandate HPV vaccination for entry into the sixth or seventh grade.

On an individual provider level, it is important to be consistent with messages to patients regarding the safety, efficacy, and importance of HPV vaccination. Physicians should take extra measures to ensure adolescent follow-up with vaccination and to increase patient awareness of payment options that make HPV vaccines available to uninsured individuals and children on public health insurance plans, such as Medicaid and SCHIP.

**References**

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