Issues in Human Papillomavirus Vaccination in Adolescents

New prophylactic vaccines against human papillomavirus (HPV) are considered a monumental feat in the world of infection-related cancers. Not since the development of the hepatitis B vaccine has the world been offered a means of protection against a cancer. The benefits of these vaccines are clearly greater than those that could have been envisioned. Although cervical cancer remains one of the top killers of women worldwide, oncogenic HPV types 16 and 18 are also key players in other anogenital cancers. Recent information expands this list to include oral cancers.

Numerous HPV epidemiology studies have underscored the common nature of HPV in sexually active individuals, including adolescents. Most data suggest that adolescents and young women are most vulnerable, with high rates of infection seen shortly after the onset of sexual activity. Geographic variability in HPV prevalence is likely caused by a number of factors, including age at first intercourse, sexual networks, and social cultures. In monitoring vaccine efficacy, it will be essential to determine accurate estimates of HPV prevalence, specifically in adolescents, as they are the primary targets of national immunization strategies. This is also true for adolescents who have already initiated sexual activity. The new vaccines are not therapeutic; thus adolescents already infected with HPV vaccine types will not receive protection. Regardless of vaccine implementation, screening for cervical cancer remains essential, as only two oncogenic HPV types are included and many sexually active adolescents may have been exposed before vaccination. However, new data regarding the natural history of HPV have impacted screening and triage guidelines, specifically in young women. Our improved understanding of natural history data has resulted in more intense intervention in older adults and more conservative management in female adolescents and younger girls. The implementation of vaccines is also affected by barriers to vaccine provision related to attitudes of both physicians and patients. Logistical considerations also should be taken into account for providers and their practices.

This supplement to the Journal of Adolescent Health reviews several important aspects related to vaccination implementation and monitoring: (1) worldwide estimates of HPV prevalence in adolescents and young women, (2) current HPV vaccine development strategies, (3) cervical screening and triage recommendations for adolescents, (4) benefits of vaccination for conditions other than cervical cancer (specifically, HPV-associated oral cancers), and (5) potential logistical barriers to HPV provision with clinical settings.

The paper by Smith and colleagues is an in-depth, thorough review of global data on age-specific prevalence of HPV infection [1]. Although this systematic review is primarily descriptive, it reflects critical pre-vaccination data, allowing comparisons in the post-vaccination era. Such data can not only be used to show evidence of vaccine efficacy but can also inform countries as to what age group is best to vaccinate. Data in this review were considered largely representative of population-based samples; in these studies the majority of women in the studies were required to have normal cytologic findings, and no study was limited to women with cervical neoplasia or cancer.

One of the findings of this study was the differences noted by geography for lower-risk populations worldwide. “Lower risk” in these cases excludes those individuals seropositive for human immunodeficiency virus (HIV), attending sexually transmitted infection (STI) clinics, or immune compromised. Central and South America showed the highest rates of infection in adolescents, with rates up to 74%. These rates may not be too surprising, because cervical cancer remain rates quite high in both Central and South America. However, in some studies, African countries with equally high rates of cervical cancer had somewhat lower rates of HPV infection. The highest reported prevalence (55%) was in 14–20-year-olds from a rural community in Mozambique. Asia tended to have the lowest prevalence rates overall, although there were distinct differences between geographic areas. However it should be emphasized that most of the data from Asia did not include adolescents. North American rates showed relatively high prevalence rates close to those in Central and
South America. Interestingly, Europe had relatively lower rates than North America in most studies, with a peak prevalence of 14% in adolescents and young women. The differences noted are likely due to differences in sexual behavior of both the woman herself and her sexual partner. However, given that HPV infection is highly transmissible and is not necessarily limited to high-risk sexual networks, differences in HPV prevalence rates across geographical regions are not as striking as those noted for other STIs such as HIV.

Most countries showed that the highest prevalence was in young women less than 20 years of age; generally, prevalence declined with increased age. However, the US and other countries found the peak at approximately 20–25 years of age, after onset of sexual intercourse. Some countries, specifically in Asia, showed a relatively constant prevalence with no peaks. A fourth pattern was U-shaped, with prevalence in older women rising almost equal to that of younger women; this was common in Central and South America. This information will be important for countries defining ages to vaccinate.

Most countries where HPV 16 and 18 data were available noted that HPV 16 and 18 comprise approximately one quarter of the overall prevalence. Although there are few remaining studies that focus on HPV 16 and 18 infection prevalence, postvaccination studies will likely incorporate data on HPV 16- and 18-associated cervical intraepithelial neoplasia (CIN). These data underscore the importance of vaccinating pre-sexually active children worldwide in the public sector, as the current vaccines are not therapeutic.

The article by Gillison illustrates the propensity for HPV to induce cancer at mucosal sites [2]. In reviewing the natural history of HPV infection, it is not at all surprising that HPV is associated with oral cancers. Certainly HPV is a sexually transmitted infection, and oral sex is commonly practiced by many couples. In addition, mucosal sites have long been known to be vulnerable to HPV infection. Metaplastic tissue, which is thought to be the primary target for HPV, is found in certain mucosal areas such as the tonsillar crypts. One may ask, “So why is this association discovered only now?” First, the association between head and neck cancers and HPV was made several decades ago [3]. The association was likely overshadowed by the enormous number of studies involving cervical cancer. Early studies of oral cancer also did not inquire into oral sex practices, for reasons that are not clear; however, societal perceptions of morals or denial may have played a role. Many individuals continue to believe that oral sex is “safe sex”; unfortunately, many STIs can be transmitted during oral sex. In the literature, most studies obtained oral samples from the buccal mucosa rather than tonsillar tissue. The review by Gillison suggests that HPV-associated cancers in the oropharynx are more likely to be in either the palate or tonsillar areas. Few studies have examined the prevalence of tonsillar HPV infections. Interestingly, HPV 16 contributes to a higher proportion of HPV-associated oropharyngeal cancers than cancers of the cervix. Among the HPV-associated tumors, HPV 16 may represent 93% of HPV-positive oropharyngeal tumors [4], relatively higher than 50% of HPV-positive cervical cancers. The reasons for these discrepancies are unclear and will require further investigation. Nonetheless current vaccine formulations that contain HPV 16 and 18 have the potential to impact these cancers tremendously; to be effective, however, the timing of vaccination will be important. Although sexual transmission is implicated in these oropharyngeal cancers, it has not yet been proved. Several studies have shown that HPV is commonly transmitted from the mother to the infant’s nasopharyngeal and buccal mucosa during birth. HPV transmission to the mouth appears to continue during infancy. In the Finnish HPV Family study [5], infants were tested beginning at birth and up to 2 years of age (specifically, at 1, 2, 6, 12, and 24 months); HPV was detected in 12–21% of oral samples at any one point over a 26-month period. Overall, oral HPV infections were estimated to be acquired by 42% of infants, of which 10% showed persistence. Persistent oral HPV infection in the infant was associated with persistent oral HPV infection in the mother. The study did not test for tonsillar or palate HPV infections. On the other hand, Gillison’s review underscores the associations found between these oropharyngeal cancers and oral sex. This suggests that tonsillar infections are likely associated with oral sex and not perineal transmission. Furthermore the onset of oral sex is common in adolescents, so vaccination will also be important in young adolescents aged 11–12 years [6,7]. Clearly it will be difficult to assess the efficacy of the vaccine in clinical trials, because these HPV-positive oropharyngeal tumors are rare.

Given the importance of continuing cervical cancer screening within the HPV vaccine era, Widdice and Moscicki outline essential aspects related to cytologic testing, colposcopy, and HPV testing in adolescents, because guidelines are distinct from those for older women [8]. This review provides an essential background on HPV virology and differences in oncogenicity between specific HPV types, and highlights the finding that cervical neoplasia is more likely to regress if detected in younger versus older women.

Among sexually active women, the risk of acquiring an HPV infection is notably high, with a median rate of estimated HPV acquisition within 3 years of first sexual intercourse. The mechanism by which HPV induces abnormal cervical neoplasia is similar among younger and older women; in brief, it is characterized by HPV infection of the basal epithelium, development of a persistent HPV infection, and expression of viral E6 and E7 oncogenes, which result in abnormal cytologic changes. The distinction between precancerous, high-grade cervical neoplasia from benign, low-grade neoplasia with a higher risk of regression is important. The higher risk of regression of cervical neoplasia in younger compared with older women is likely influenced by the natural history and timing of infection. Younger women more likely reflect a recent infection that is more easily cleared by the immune response. Older women with neoplasia more often reflect persistent HPV infection, which, by definition of its persistence, has already successfully evaded the immune response. In light of these differences in the natural history of HPV and cervical
neoplasia, clinical management guidelines have been modified to address differences in the risks and benefits of screening and treatment in younger, sexually active females. For example, an important distinction is that women 20 years or younger with a low-grade squamous intraepithelial lesion or atypical squamous cells of undetermined significance (ASCUS) are recommended for follow-up with a cytologic smear repeated at 12-month intervals rather than referral for immediate colposcopy as for women more than 20 years of age. Furthermore HPV-DNA testing is not recommended for young women less than 21 years of age for the triage of ASCUS cases, nor for women less than 30 years of age as a means of primary screening. As HPV vaccines become more widely available through population-based implementation and our understanding of the natural history of HPV and cervical neoplasia infections improves, further changes to existing clinical guidelines are expected.

Clearly, proper dissemination of the HPV vaccine will affect vaccine efficacy on the population level. Vaccination success takes a community effort, with dissemination of information for both providers and recipients, decreasing patient barriers such as cost and availability, and educating providers about the efficacy of the vaccine and information regarding questions that might arise. Although most studies of barriers have focused on parental obstacles, the study by Keating and colleagues examined logistical barriers for healthcare providers [9]. This paper examined concerns of healthcare providers in a geographic area in the Southern United States. Not surprisingly, most of the obstacles related to inadequate reimbursement through insurance companies or governmental agencies. In addition to inadequate reimbursement, the burden of determining eligibility by individual insurance companies was also reported as a major obstacle. One report of concern was that of the drug representative telling providers to instruct their patients to research their own coverage. Barriers such as these may become insurmountable for most adolescents seeking care, and underscore the potential lack of knowledge regarding providers’ needs. The study did not include attitudes of providers toward the vaccine (i.e., regarding safety or efficacy) and who should or should not have the vaccine. Certainly, negative attitudes may influence respondents’ answers. Obstacles to HPV provision identified in this study continue to add to the “time element” of providing the new HPV vaccine. Despite the widespread advertisement of the vaccine, parents and adolescents still need to become better informed. Compared with other vaccines, this vaccine requires substantial additional physician time to answer many of the questions presented by parents and youths. Better efforts to educate families are needed.

The provision of both prophylactic and therapeutic vaccinations for the prevention and treatment of HPV infection will be critical for the global reduction of mortality associated with cervical cancer and HPV-associated cancers. The article in this supplement by Moscicki provides a comprehensive overview of two currently available HPV prophylactic vaccines licensed in geographical areas worldwide, and summarizes current clinical development efforts for future therapeutic HPV vaccines. HPV infection has an extraordinary way of evading the host’s immune response during a natural infection, resulting in an absence of lytic activity and thus little inflammation. Both innate and adaptive cell-mediated immune responses appear to be necessary for effective clearance of the HPV virus.

Notably, CD4+ and CD8+ T cell responses to E6 and E7 (and likely to other HPV proteins, including E2, E4, E5, and L1/L2) appear critical for viral clearance.

For prophylactic protection, the two currently available prophylactic L1 virus-like particle vaccines are able to effectively induce neutralizing antibody titers (which are considerably higher than those induced within natural infections) and cell-mediated immunity, resulting in protection against persistent infection and associated cervical neoplasia attributable to HPV vaccine types. Data clearly indicate that these vaccines do not induce protection among women who are current carriers of HPV vaccine types, and thus optimal protection is ensured if vaccination is given before the age of first sexual intercourse. However, because of relatively small sample sizes, further data are needed to clarify whether women who have been exposed to HPV vaccine types and have later cleared their infections (i.e., HPV vaccine type seropositive/DNA negative) will receive subsequent protection from vaccination. Novel second-generation vaccination formulations and modes of delivery will certainly affect not only overall HPV vaccine production costs but also advance provision and distribution options for HPV vaccines to the wider community.

As available L1 prophylactic vaccines have shown no evidence of producing a therapeutic effect, current efforts to develop therapeutic vaccines could make an immediate difference. At present, most therapeutic vaccines in development aim to upregulate cell-mediated immune responses, largely focusing on E6 and E7 oncoproteins.

A number of different approaches are being used to develop successful HPV therapeutic vaccines, including DNA and peptide-DNA, protein-based, viral-based, and chimeric-based strategies, although the world still waits for the development of an effective therapeutic vaccine. Given the notable burden of cervical cancer and the obstacles in establishing efficient cervical cancer screening and treatment programs in many less-developed countries, as well as the economic burden of HPV-associated clinical outcomes in developed countries, the needs for incorporating such vaccines are paramount.

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References


