Updates on HPV Immunizations

- ***Kenneth A. Alexander, M.D., Ph.D.***

Papillomaviruses are small unenveloped double-stranded DNA viruses that cause species- and tissue-specific diseases in virtually all vertebrates. Papilloma-viruses appear to have co-evolved with homo sapiens from the time that we shared a common ancestor with birds.[1] In humans, more than 200 human papillomavirus (HPV) types have been identified. The HPVs are classified according to their tropism for either keratinized skin or mucous membranes. Mucous membrane-associated HPV types are further subclassified as high risk or low risk according to their proclivity for causing malignant transformation of epithelial cells. HPVs chronically infect the skin and the mucous membranes of the respiratory and anogenital tract. HPV infections are maintained in keratinocytes in the basal layer of the skin or mucous membrane. As the basal keratinocytes begin their differentiation into squamous epithelial cells, viral DNA replication is triggered. HPV virion assembly occurs as the keratinocytes complete their differentiation into squamous epithelial cells.[2]

Human Papillomavirus

Mature HPV virions are found on the surface of the skin and mucous membranes; therefore, HPV infections are transmitted very effectively by direct or indirect skin-to-skin or mucous membrane-to-mucous membrane contact. Because HPV transmission occurs by contact, they are among the most egalitarian of all infections. HPV infections occur commonly in all social classes and ethnic groups. In North America and Europe, it is estimated that an individual's lifetime risk of a genital HPV infection exceeds 75%.[2] While most cutaneous HPV infections are acquired in childhood, and while most infections with mucous membrane-associated HPV types occur during adolescence and young adulthood, new HPV infections occur across the lifespan.[3,4]

The majority of HPV infections are of little or no consequence; people become infected, never know that they are infected with an HPV, and over a period of weeks to months, clear their infection. Only a minority of individuals go on to suffer the complications of persistent HPV infections. While risk factors for progression from infection to malignancy have been identified (eg, cigarette smoking, immune compromise),[3,4] most patients with HPV-associated malignancies lack significant risk factors.[5]

HPV Vaccines

HPV-associated diseases and their associated HPV types are listed in Table 1. The vaccine efficacies for prevention of vaccine type-specific dysplastic conditions by the commercially available HPV virus-like particle vaccines are shown in Table 2. Taken together, the data indicate that the bivalent and quadrivalent HPV vaccines, given prior to acquisition of HPV infection, can prevent from 98% to 100% of CIN2/3, and the quadrivalent vaccine can prevent 100% of VIN2/3, 100% of VaIN2/3, and 75% of AIN2/3. The quadrivalent vaccine, because it contains antigen for HPV6 and HPV11, can prevent 90% of genital warts.[6]

Table 1. Malignancies and Their Associated HPV Types

Malignancy	% HPV-associated	Most commonly-associated HPV types
Cervical cancers	99.7%	16, 18, 31, 33, 45, 52, 58
Vaginal cancers	74%	16
Vulvar cancers	30%	16, 18, 33
Anal cancers	88%	16, 18
Penile cancers	63%	16
Head and neck cancers*	40%	16

*Oropharynx, larynx and hypopharynx, and oral cavity.

Source: Wieland U, et al. *N Engl J Med*. 2015:372:2566-2569; Hamlish T, et al. *Vaccine*. 2012;30(45):6472-6476. Giambi C, et al. *BMC Infect Dis*. 2014;14:545; http://www.cdc.gov/pertussis/downloads/pertuss-surv-report-2013.pdf; http://www.cdc.gov/abcs/reports-findings/surv-reports.html; http://www.cdc.gov/STD/HPV/STDFact-HPV.htm.

Table 2. Protocol Efficacy for Prevention of HPV-associated Conditions Due to Vaccine-type HPVs (Quadrivalent Vaccine)

Females	
CIN2/3	97% to 100%
VIN2/3	100%
VaIN2/3	100%
Genital warts	98%
Males	
Genital warts	90%
AIN2/3	75%

Key: CIN, cervical intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia; VaIN, vaginal intraepithelial neoplasia; AIN, anal intraepithelial neoplasia

Source: Bosch FX, et al. *Dis. Markers*. 2007;23(4):213-227.

Because HPV16 and HPV18 account for only 70% of cervical cancers and other anogenital malignancies, the manufacturer of the quadrivalent vaccine recently sought and gained the Food and Drug Administration (FDA) approval for marketing of a 9-valent vaccine. With the inclusion of antigens for an additional 5 oncogenic HPV types (HPV types 31, 33, 45, 52, and 58), the 9-valent vaccine offers increased protection against a broader array of HPV-associated malignancies (Table 3). As with the bivalent and quadrivalent HPV vaccines, the 9-valent vaccine has very high efficacy (96.7%) for prevention of the composite endpoint of HPV-associated dysplasias and malignancies (CIN2/3, AIS, cervical cancer, VaIN2/3, vaginal cancer, VIN2/3, and vulvar cancer) due to HPV types 31, 33, 45, 52, and 58.[7]

Table 3. Estimated Type Contribution for HPV-related Malignancies

Malignancy type	Proportion of disease attributable to HPV types 6, 11, 16, 19	Proportion of disease attributable to HPV types 6, 11, 16, 18, 31, 33, 45, 52, 56
Cervical cancers	70%	90%
Vaginal cancers	65%	85%
Vulvar cancers	75%	90%
Anal cancers	85%	90%

Source: de Sanjose S, et al. *Lancet Oncol*. 2010;11(11):1048-1056; de Sanjose S, et al. *Eur J Cancer*. 2013;49(16):3450-3461; Alemany L, et al. *Eur J Cancer*. 2014;50(16):2846-2854; http://www.cdc.gov/nchhstp/newsroom/docs/std-trends-508.pdf.

All 3 HPV virus-like particle vaccines have similar safety profiles.[8–10] Both prelicensure and postmarketing studies show that these vaccines are generally safe; the most common adverse events associated with immunization are local site reactions (pain, swelling, and erythema). Most local-site reactions are mild. Some HPV vaccinees experience transient low-grade fevers and myalgias following immunization. As with other vaccines given to adolescents, HPV vaccines have been associated with post-immunization syncopal episodes. These syncopal episodes have been attributed to the immunization process, rather than to vaccine antigens.[8,9]

Recommended HPV Immunization Schedule

Based on the clinical trials proven efficacy and safety of HPV vaccines, the US Advisory Committee on Immunization Practices (ACIP) recommends immunization of all males and females ages 11 to 12 years with a 3-dose HPV vaccine series; females may receive either the bivalent, quadrivalent, or 9-valent vaccine and males should receive the quadrivalent or 9-valent vaccine. Because HPV vaccines are a part of the larger platform of vaccines recommended for adolescents, the HPV series may be initiated as young as 9 years old. Catchup immunization of females is recommended through 26 years of age; catchup immunization of males is recommended through 21 years of age, except

for males at high risk of HPV-associated malignancies (men who have sex with men, and males with HIV infection), for whom immunization is recommended through 26 years of age.

Despite strong and unequivocal recommendations from the AICP, HPV vaccine acceptance in the United States represented a challenge. The National Immunization Survey-Teen found that, in 2014, only 39.7% of vaccine-eligible females ages 13 to 17 years had completed the recommended 3-dose series. Immunization rates in males were found to be lower: only 21.6% of vaccine-eligible males ages 13 to 17 years have completed the 3-dose series.[10] The future human costs of HPV underimmunization will be high. If this trend continues, and as unvaccinated adolescent females move into the age of cervical disease, nonimmunizing providers will contribute to 7000 preventable cases of cervical cancer and 2200 preventable cervical cancer deaths annually. Given that the ACIP has recommended universal immunization of 11- to 12-year-old females since 2006, we can already attribute more than 20,000 future preventable cervical cancer deaths to our inability to immunize effectively. And this is only the beginning, as this calculation makes no account for disease in males, anal disease, or downstream complications of cervical disease, such as prematurity or infertility. Furthermore, given the increasing incidence of HPV-associated head and neck malignancies in males, and the low rate of male HPV immunization, it is likely that as many or more men than women will face surgery or die from head and neck malignancies in the coming years.

Improving Immunization Rates

Why are HPV immunization rates so low in the United States (especially when immunization rates are compared with those of other nations (Table 4)? While it is tempting to exclusively place the blame on parents who fear that immunization will change the behavior of their children, or blame the many misguided authors of internet pages and blogs that trumpet the dangers of HPV immunization, there is now an evolving body of data suggesting that low HPV immunization rates are related, for the most part, to the inability or unwillingness of some health care providers to advocate effectively. Gilkey et al.[11] found in a national online survey of 776 pediatricians and family practice physicians that 27% of respondents stated that they did not strongly endorse HPV immunization, or deliver timely recommendations for girls (26%) or boys (39%). Approximately 59% of physicians used a risk-based approach to recommending HPV immunization, and only 51% usually recommended same-day immunization. Similarly, Clark and Kuter, using audio recordings of pediatric well-visit encounters with girls 11 to 12 years of age and boys 11 to 18 years of age, found that in 82% of visits, adolescent vaccines were mentioned; in 75% of visits, HPV vaccines were mentioned specifically. The most commonly used recommendation strategy (72% of the time) was detailed discussion (HPV vaccine discussed with greater detail than other adolescent vaccines); same day immunization rate resulting from this strategy was 38%. Brief mentions (HPV vaccine mentioned without a recommendation or direction), on the other hand were used 17% of the time with a same-day immunization rate of 27%. Interestingly, while routine recommendations (HPV vaccine recommended the same as other adolescent vaccines, 11%), were the least used strategy, this approach resulted in a same-day immunization rate of 94%. Thus, we need to exchange droning discussions about HPV immunization for a simple statement that the vaccine is recommended and should be given today.

Table 4. Estimated 3-dose HPV Vaccine Coverage of Vaccine-eligible Females* by Country[33-38]

Country	3-dose completion rate (year assessed)
Australia	71% (2009), 73.1% (2014)
Belgium	82% (2010)
Canada	50% to 86% (varies by province)(2009)
Denmark	58% (2010), 79% (2011)
France	24% (2008), 25%-29% (2012)
Italy	35% (2009), 65% (2011)
Mexico	67% (2010)
Netherlands	58% (2010)
New Zealand	40% (2010)
Norway	63% (2011)
Panama	67% (2010)
Portugal	84% (2011)
Rwanda	93% (2011)
Slovenia	55% (2011)
Spain	64% (2011), 71% (2012)
United Kingdom	84% to 92% (2009)
United States	32% (2010), 37% (2013), 40% (2014)

*Excluding catch-up cohort, if applicable

Source: Alemany L, et al. *Int J Cancer*. 2015;136(1):98-107; de Sousa ID, et al. *BMC Urol*. 2015;15:13; Ndiaye C, et al. *Lancet Oncol*. 2014;15(12):1319-1331; http://www.hpvcentre.net/summaryreport.php; http://www.hpvregister.org.au/research/coverage-data/HPV-Vaccination-Coverage-2014; http://ecdc.europa.eu/en/publications/Publications/20120905_GUI_HPV_vaccine_update.pdf.

That provider recommendation is a major determinant of vaccine acceptance comes as no surprise. The importance of provider recommendation for immunization has been recognized for a long time. The same applies for HPV immunization. Many studies have shown that a strong provider

recommendation increases vaccine acceptance.[12–15] While many studies also cite parental HPV education as a supporter of vaccine acceptance, such education is difficult to disentangle from the education given by a recommending provider.

It may also be that providers are conveying the wrong type of HPV immunization messaging to families. For most immunization advocates, there is a belief (as evidenced by the panoply of community HPV immunization education programs offered) that if sufficient information is provided to parents, then parents will make the right decision to accept immunization for their children.[13] Unfortunately, many of these conversations are poorly managed by physicians.[14] Emerging are notions that long-winded and complex explanations of HPV epidemiology and vaccinology may be self-defeating, and that “less is more” when discussing HPV immunization of adolescents.[15,16] Some experts have suggested that the entire initial HPV immunization conversation should be as simple and direct as “It’s time for your child’s HPV vaccine. Which arm?” When parents ask questions, the provider should reassure parents in simple and direct terms that HPV immunization is effective for prevention of cancers in adulthood, is safe, and is recommended strongly by the immunizer and the immunizer’s practice.[17,18]

There is also evidence suggesting that immunizers undervalue HPV immunization as a means for preventing future mortality and morbidity. Gilkey et al.,[15] using a national sample of 776 US physicians (53% pediatricians, 47% family medicine physicians) assessed physicians’ perceptions and communication practices related to recommending adolescent vaccines for 11- and 12-year-old patients. While 73% of physicians reported recommending HPV vaccine as highly important for patients, 11 to 12 years of age, physicians recommended tetanus, diphtheria, and acellular pertussis (Tdap) (95%) and meningococcal vaccines (87%) as highly important for this age group. Only 13% of physicians perceived HPV vaccine as being highly important to parents, which was far fewer than perceived parental support for Tdap (74%) and meningococcal vaccines (62%, both $P<.001$). Among physicians with a preferred order for discussing adolescent vaccines, 70% discussed HPV vaccine last.

While it was hoped that school requirements for Tdap and meningococcal conjugate vaccine (MCV4) immunization might also increase rates of HPV immunization, this appears not to be the case. There is little, if any, correlation between uptake of Tdap and MCV4 vaccines and HPV vaccine uptake. While the reasons for this poor correlation are unknown, the data does demonstrate that there are many missed HPV immunization opportunities. Further, it is suggested that physicians and parents undervalue HPV vaccination relative to Tdap and MCV4 immunization, if for no other reason than that Tdap and MCV4 may be required for continued school matriculation (ie, if one vaccine is required for school attendance and another is not, then the required vaccine must be more important). Indeed, at the early adolescent health care visit, many health care providers will offer immunization with Tdap and MCV4 vaccines, while reserving HPV immunization for “later”. Similarly, many parents at the early adolescent visit will ask their child’s provider to “give what’s required” for continued matriculation at school. Unfortunately, parents and providers confuse what is required for school with what is most important for protection of adolescents. In the United States, pertussis kills approximately 20 people per year, mostly young infants;[19] meningococcal infections kill approximately 100 people each year.[20] Therefore, by administering Tdap and MCV4 vaccines, we

are working to prevent approximately 120 fatalities per year. In comparison, each year in the United States, approximately 4000 women die of cervical cancer, another 1900 die of vaginal and vulvar cancer, 1000 men and women die of anal cancers, and 1700 die of HPV-associated oropharyngeal cancers. Taken together, timely HPV vaccination could prevent approximately 10,000 HPV-associated cancer deaths. By administering Tdap and MCV4 while delaying (or never giving) HPV vaccines, we are trading gold for brass. HPV, Tdap, and MCV4 all need to be given at 11 to 12 years of age.

Fortunately, the low rates of HPV immunization in the United States are not seen in most developed and even in some developing countries. Shown in Table 4 are the rates of HPV immunization in a sample of countries from around the world. With few exceptions, most successful national HPV immunization programs are school-based. These school-based national immunization programs provide cost-effective immunization of large numbers of girls (and now, in some countries, to boys).

Perhaps one of the greatest challenges to effective HPV immunization has been the stigmatization of HPV infection. Clinicians are quick to point out that HPV infections are sexually transmitted. By identifying HPVs as sexually transmitted, HPV infections are, in peoples' minds, associated with "notorious" sexually transmitted infections, including gonorrhea, syphilis, and chlamydia. Because there is, in all societies, intense stigmatization of gonorrhea, syphilis, and chlamydial infections, HPV infections are, by association, treated as equally notorious. What follows is a morality judgment; HPV infection is all-to-frequently treated as a moral failure. And yet, the annual number of new HPV infections is 10 times higher than the rate of new chlamydial infections, 42 times higher than the rate of new cases of gonorrhea, and 800 times higher than the rate of new syphilis cases.[21,22]

A re-examination of how we think about HPV infections is proposed. Perhaps, given that in our society the lifetime risk of a genital HPV infection is 70% to 80%, we should view HPV infection as normal (certainly, it is in a statistical sense; we set that cutoff at 2 standard deviations from the mean, or 5%), and given that the risk of progression to malignancy is low, we should move HPV infection in our minds from the company of other sexually transmitted infections to the category of normal human flora. As with the staphylococci that colonize our skin, and as with the streptococci that colonize our aerodigestive tracts, HPVs colonize our anogenital and aerodigestive areas. While a small minority of people experience serious staphylococcal or streptococcal infections, most of us live with our staphylococcal and streptococcal flora, unaware of their presence and without serious incident. Likewise, with HPV infections, most of us are unaware of our infections; we live with our HPV infections with neither knowledge nor indication of their presence. Only a minority of us goes on to develop HPV-associated dysplasias, and a still smaller proportion of us develop an HPV-associated malignancy.

We still have much to learn about immunizing adolescents, and how to promote adolescent immunization effectively to keep our sons and daughters healthy as they move into adulthood. The availability of highly effective HPV vaccines is providing us a tremendous opportunity to learn, because HPV vaccines are a bellwether for the future of immunization. We all look forward to a time when we can vaccinate to prevent infections due to human immunodeficiency virus, hepatitis C virus, human cytomegalovirus, herpes simplex viruses, *Neisseria gonorrhea*, *Chlamydia trachomatis*, syphilis, and Group B *Streptococcus*, as well as to vaccines for prevention breast cancer,

melanoma, and prostate cancer. What must be noted is that each of these vaccines, if and when they become available, will likely be administered to adolescents and young adults. Thus, I believe that the future of immunization is not babies; the future of immunization owns a cell phone. And, as with HPV vaccines now, in the future, we will be immunizing adolescents against diseases most of which are inextricably intertwined with human sexuality. My concern is that, were we to have an effective HIV or HSV vaccine available to us today, many parents would say “not my son” or “not my daughter”, and many providers would say “not my patients.” Thus, to prepare us for the vaccines of the future, the HPV vaccines of today should be viewed as an opportunity to learn how to immunize adolescents effectively. The HPV vaccines of today must be used as an opportunity for us to get better at adolescent immunization.

Summary

What must we learn to move successfully into this new world of adolescent immunization? We must learn that risk-based immunization is a failed strategy that leaves our young people unimmunized and at risk of disease. We must learn to be less afraid of what parents might think when we give a recommendation that benefits their children, even if we have to admit that most humans eventually become sexually active. We must learn to recommend, rather than to judge. We must learn to be less wordy and hesitant, and be more direct, succinct, and strong in our recommendations. We need to believe that we are protecting our children so that they will become healthy adults. Only then can we effectively prevent disease in adulthood by immunizing in adolescence.

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