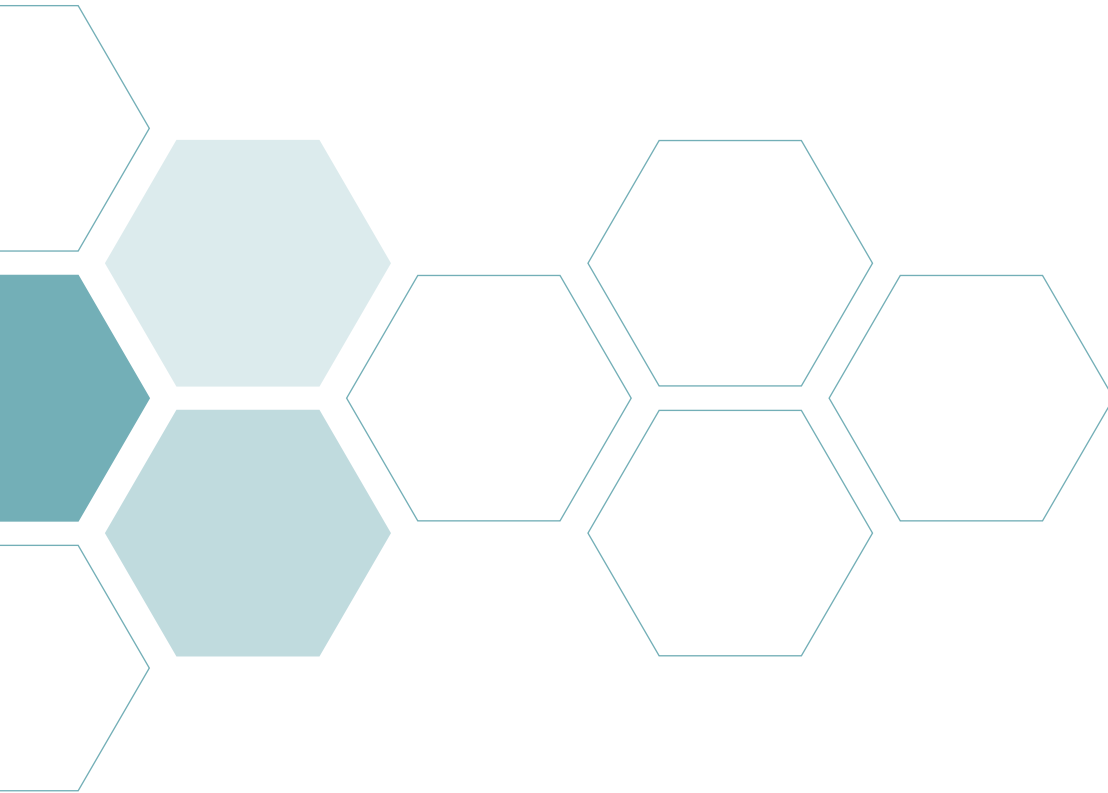




Managed Care Consideration in Human Papillomavirus (HPV): Overcoming Barriers to Improved Patient Outcomes

A CME/CNE Approved Activity



JOURNAL of **MANAGED CARE MEDICINE**

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Managed Care Consideration in Human Papillomavirus (HPV): Overcoming Barriers to Improved Patient Outcomes

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Glen Allen, VA 23060

Authors:

Kenneth A. Alexander, MD, PhD is Chief of the Division of Infectious Diseases at the Nemours Children's Hospital and is a Professor of Pediatrics at The University of Central Florida College of Medicine in Orlando, FL. Amanda F. Dempsey, MD, PhD, MPH is an Associate Professor of Pediatrics at the University of Colorado Denver Children's Outcomes Research Program and a Primary Care Pediatrician at Children's Hospital Colorado in Aurora, CO.

Gary M. Owens, MD is President of Gary Owens and Associates in Ocean View, DE.

Learning Objectives:

1. Review the prevalence of HPV infection, the types of cancers it causes and the impact of HPV vaccination in the United States.
2. Assess the latest clinical data regarding the impact of HPV vaccination on relevant clinical endpoints.
3. Identify perceived barriers by both healthcare providers, managed care professionals and patients to HPV vaccination.
4. Implement strategies to overcome perceived barriers to HPV vaccination in the pediatric, adolescent and/or adult clinic setting.
5. Evaluate the value of concise and consistent communication to educate patients and/or caregivers on the importance of completing the HPV vaccination series.
6. Examine the evolving role of HPV vaccinations in adults.

Faculty Disclosure:

Dr. Alexander is a speaker on behalf of Merck Vaccines and MSD and has participated on advisory boards for Merck Vaccines and MSD.

Dr. Dempsey has disclosed no relevant financial relationships.

Dr. Owens has no relevant financial relationships to disclose.

All material has been peer reviewed for bias.

Planning Committee Disclosure

Bill Williams, MD; Jacqueline Cole, RN, MS, CPHQ, CMCN; and Jeremy Williams have no relevant financial relationships to disclose.

Accreditation and Designation

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Managed Care Consideration in Human Papillomavirus (HPV): Overcoming Barriers to Improved Patient Outcomes

Post-Test Questions

- Peak prevalence of HPV infection typically occurs within the ____ decade after sexual activity begins?
a. First b. Second c. Third d. Fourth
- For both men and women, the lifetime risk of an anogenital HPV infection is estimated at _____.
a. 10 to 20% b. 30 to 40% c. 70 to 80% d. 90 to 100%
- Which of the following cancers is NOT associated with HPV infection?
a. Penile b. Liver c. Vulvar d. Oropharyngeal
- Which HPV type is the cause of 50% of cases of cervical cancer?
a. 6 b. 11 c. 13 d. 16.
- Which of the following is the efficacy of 9-valent HPV vaccine for preventing cervical intraepithelial neoplasia Grade 2 or higher due to HPV vaccine types among HPV-naïve populations?
a. 30% b. 60% c. 80% d. 97%
- Which cancer(s) is Gardasil® 9 FDA approved for preventing in males?
a. Penile and oropharyngeal b. Anal
c. Penile d. Anal, penile and oropharyngeal
- Which cancer(s) is Gardasil® 9 FDA approved for preventing in females?
a. Anal, cervical, vaginal, and vulvar cancer
b. Cervical
c. Cervical, vaginal, vulvar
d. Cervical and oropharyngeal
- According to the ACIP immunization recommendations, which of the following patients should receive the HPV vaccine?
a. Female aged 8 years
b. Male aged 35 years who has sex with other men
c. Male aged 11 years
d. Female with prior history of cervical intraepithelial neoplasia grade 1
- Which of the following is the most common adverse effect with the HPV vaccine?
a. Syncope b. Injection site reaction
c. Headache d. Fever
- Which of the following is a communication strategy for use with a reluctant parent and/or patient?
a. Strong presumptive blanket recommendation
b. Face-to-face education
c. Motivational interviewing
d. Correcting knowledge gaps

Activity Evaluation and Improvement Process

*Please rate this activity on the following scale:
4 - Excellent 3 - Good 2 - Fair 1 - Poor*

- Based on the content presented, I am better able to:
Review the prevalence of HPV infection, the types of cancers it causes and the impact of HPV vaccination in the United States.
4 3 2 1
Assess the latest clinical data regarding the impact of HPV vaccination on relevant clinical endpoints.
4 3 2 1
Identify perceived barriers by both healthcare providers, managed care professionals and patients to HPV vaccination.
4 3 2 1
Implement strategies to overcome perceived barriers to HPV vaccination in the pediatric, adolescent and/or adult clinic setting.
4 3 2 1
Evaluate the value of concise and consistent communication to educate patients and/or caregivers on the importance of completing the HPV vaccination series.
4 3 2 1
Examine the evolving role of HPV vaccinations in adults.
4 3 2 1
- The activity and presenters were free of bias.
4 3 2 1
- The activity was applicable to my position.
4 3 2 1
- How confident are you in managing patients based on this activity? (4 very confident - 1 not confident)
4 3 2 1
- Do you plan to change management strategies or patient care in your organization or practice based on the content presented?
 Yes No
- If yes, what changes do you plan to implement in management strategies or patient care in your organization or practice?

- Did the content of the activity help in meeting your above goal?
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fax (804) 747-5316

EDITOR-IN-CHIEF
J. Ronald Hunt, MD

PUBLISHER
Jeremy Williams

JOURNAL MANAGEMENT
Douglas Murphy
Communications Inc.
P.O. Box 71895
Richmond, VA 23255-1895
(804) 387-7580
fax (703) 997-5842

MANAGING EDITOR
Barry Barnum
barry.barnum@douglasmurphy.com

GRAPHIC DESIGN
Douglas Murphy Communications, Inc.

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jwilliams@namcp.org,
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Managed Care Consideration in Human Papillomavirus (HPV):

Overcoming Barriers to Improved Patient Outcomes

Kenneth A. Alexander, MD, PhD; Amanda F. Dempsey, MD, PhD, MPH; Gary M. Owens, MD

Introduction

The human papillomavirus (HPV) is a double-stranded DNA virus that infects only humans and is associated with mild to moderate disease that even in the absence of therapy may spontaneously regress. Two hundred types of HPV have been identified.¹ Many of these subtypes cause no symptoms, while others may cause foot and hand warts. Forty of these subtypes, which affect the anogenital area, are numbered and divided into low-risk and high-risk strains. Low-risk types typically cause genital warts and the high-risk or oncogenic types increase the risk of certain cancers, which is discussed later.

Globally, anogenital HPV is the most common sexually transmitted infection. There is an estimated prevalence of 20 million HPV infections in the United States (U.S.). Peak prevalence of HPV infection typically occurs within the first decade after sexual activity begins, usually in individuals between the ages of 15 to 25 years in most western countries. Between 2013 and 2014, the prevalence among females aged 18 to 59 years was 40 percent for all HPV types and 20 percent for high-risk HPV types.² In an earlier, pre-vaccine era National Health and Nutrition Examination Survey (NHANES), which included 2,603 women aged 14 to 59 years, 30 percent had serologic evidence of prior infection with one of seven high-risk HPV types. This proportion is thought to be an underestimation of the true exposure burden, as natural infection does not always result in detectable antibody levels. Only 50 to 60 percent of women develop serum antibodies to HPV after natural infection.³ Importantly, these are only point-prevalence estimates, as lifetime risk of genital HPV infection is much higher. For both men and women, the lifetime risk of an anogenital HPV infection is estimated at 70 to 80 percent. However, many experts believe that virtually all sexually active adults have been infected by HPV because most HPV infections are transient and can come and go in the interval between HPV testing.⁴

The annual incidence of HPV infections is estimated at 5.5 million. One study of female college students reported a 29 percent one-year cumulative incidence of HPV infection following their first male

sexual partner.⁵ The cumulative incidence increased to almost 50 percent after three years. Many sexually active young women have sequential infections with different oncogenic types of HPV. Most HPV infections of the cervix are asymptomatic, and more than 90 percent of detected infections are cleared within two years.⁶ The degree of protection and duration of immunity after natural infection are not known.

HPV infection is not only a disease of young adults. A prospective population-based study of 7,237 females residing in Costa Rica that assessed persistent cervical infection with any of more than 40 HPV types showed that the risk for persistent infection increased with age.⁷ Similar findings were reported among 954 heterosexual males aged 18 to 70 years from Brazil, Mexico, and the U.S. which showed that the risk for persistent anal canal infection with any of 37 HPV types increased with age.⁸

HPV-Associated Cancers

The World Health Organization's International Agency for Research on Cancer (IARC) has classified 12 HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) among the Group 1 carcinogens.⁹ High-risk types of HPV appear to induce oncogenic changes in affected cells by integrating parts of the HPV DNA into the host DNA. HPV integration may trigger genome instability. For instance, it results in genome structure rearrangement and copy number variation. Whole-genome sequencing has shown HPV integrants flanking and bridging extensive host genomic amplifications and rearrangements, including deletions, inversions, and chromosomal translocations.¹⁰

HPV contributes to the development of cervical, anal, vaginal, vulvar, penile, and oropharyngeal cancer. It is responsible for 90 percent of anal and cervical cancers. Studies show that 70 percent of cancers of the oropharynx may be linked to HPV.¹¹ Exhibit 1 shows the estimated number of HPV-associated and HPV-attributable cancer cases per year.^{12,13}

Pediatric and family medicine providers and managed care decision makers need to understand that HPV-associated malignancies destroy lives. HPV-

Exhibit 1: Number of HPV-Associated and HPV-Attributable Cancer Cases per Year^{12,13}			
Cancer Site	Average number of cancers per year in sites where HPV is often found (HPV-associated cancers)	Percentage probably caused by any HPV type^a	Number probably caused by any HPV type^a
Cervix	11,866	91%	10,751
Vagina	846	75%	635
Vulva	3,934	69%	2,707
Penis	1,269	63%	803
Anus ^b	6,530	91%	5,957
Female	4,333	93%	4,008
Male	2,197	89%	1,949
Oropharynx	18,226	70%	12,885
Female	3,412	63%	2,160
Male	14,814	72%	10,725
TOTAL	42,671	79%	33,737
Female	24,391	83%	20,260
Male	18,280	74%	13,477

^aHPV types detected in genotyping study; most were high-risk HPV types known to cause cancer
^bIncludes anal and rectal squamous cell carcinomas

associated cancers affect younger adults more than non-HPV-associated cancers (Exhibit 2).¹³⁻¹⁵ Importantly, more than 14 percent of cervical cancers are diagnosed before age 35, 30 percent of oropharyngeal cancers before age 50, and over 30 percent of anal cancers before age 55.

Cervical cancer is the fourth most common cancer among women, with virtually all cases attributable to HPV infection. HPV 16 accounts for approximately 50 percent of cases and HPV 18 for 20 percent.¹⁶ HPV types 31, 33, 45, 52, and 58 are estimated to cause an additional 19 percent. In the U.S., the median age of cytologically detected precancerous cervical lesions occurs approximately 10 years after the median age of sexual debut.¹⁷ Cervical intraepithelial neoplasia (CIN) is the precancerous cervical lesion and is

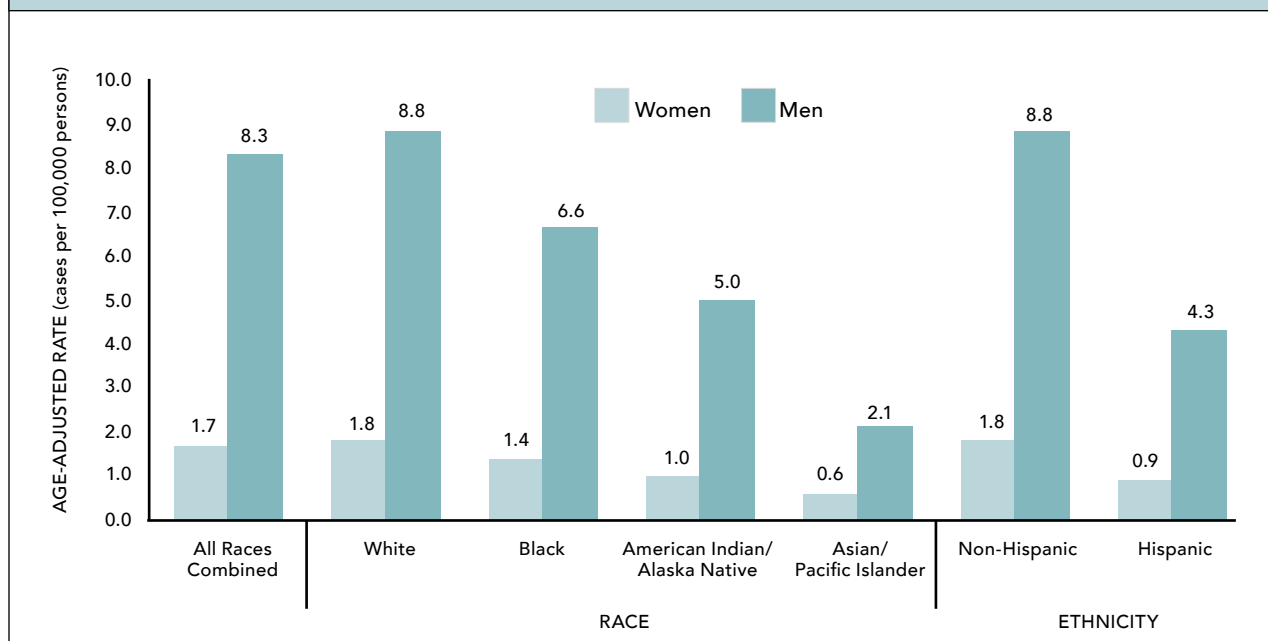
graded on a scale of 1 to 3, based on how abnormal the cells look under a microscope and how much of the cervical tissue is affected. CIN Grades 1 to 3 used to be called mild to severe dysplasia.

Many cancers of the external genitalia are associated with HPV infection. Estimates for vulvar cancer HPV association range from 29 to 69 percent overall, but is 87 percent for vulvar intraepithelial neoplasia (VIN). Most HPV-associated vulvar cancers are associated with HPV16 (85%), but a causative role for other, less frequently occurring mucosal HPV types (HPV26, 66, 67, 68, 70 and 73) has also been shown with genomic testing of tumors.¹⁸ Seventy-five percent of vaginal cancer cases are thought to be caused by HPV, with the estimate being 69 to 100 percent for vaginal intraepithelial neoplasia (VaIN). HPV 16 is the most commonly implicated type for vaginal cancer.¹⁹ HPV types 16 and 18 cause approximately 35 to 40 percent of penile cancers overall and 70 to 80 percent of HPV-positive penile cancers.²⁰

Much of the focus on HPV-related cancers has been on cervical cancers; however, there is now an increasing burden of HPV-related, non-genital cancers which has implications for at-risk patients, especially males. According to the American Cancer Society, approximately 53,000 people will get oropharyngeal cancer in 2019.²¹ An estimated 10,860 people will

Exhibit 2: Median Age at Diagnosis of Selected Cancers¹³⁻¹⁵			
Non HPV Related		HPV Related	
• Breast Cancer	62	• Cervical Cancer	47
• Colon Cancer	68 (men) 72 (women)	• Oropharyngeal Cancer	62
• Prostate Cancer	67	• HPV-related	<50
• Lung Cancer	72	• Anal Cancer	60

Exhibit 3: HPV-Associated Oropharyngeal Cancer Rates by Race, Ethnicity, and Sex, per Year, United States, 2011–2015¹³



die of these cancers. The incidence of oropharyngeal cancer among elderly patients has been growing significantly in the U.S. since 2000.²² This has been especially true for elderly men. Overall, the rates of HPV-associated oropharyngeal cancer are higher for men than women, no matter the race or ethnicity (Exhibit 3).¹³

HPV-associated oropharyngeal cancers are primarily found in the oropharynx, the base of the tongue and in the tonsils. HPV has also been linked to cancer of the larynx. HPV-related oropharyngeal cancers occur in a younger population than the non-HPV-associated cancers and are associated with sexual risk factors. Non-HPV-associated cancers are associated primarily with alcohol and tobacco use and often have a p53 mutation. In the U.S., the incidence of HPV-associated oropharyngeal cancers has been rising and the incidence of non-HPV-associated cancers has been declining.²³ In an age- and gender-matched case-control study of 130 patients with newly diagnosed squamous cell carcinoma of the head and neck, oropharyngeal malignancy was associated with high-risk sexual behaviors, oropharyngeal HPV infection, and HPV 16 seropositivity.²⁴

Anal cancer incidence rates are increasing in both men and women. The American Cancer Society estimate for anal cancer in the U.S. for 2019 is 8,300 new cases (5,530 in women and 2,770 in men) and 1,280 deaths (760 in women and 520 in men).²¹ HPV types 16 and 18 cause nearly 90 percent of anal cancers

and precancerous anal lesions (i.e., anal intraepithelial neoplasia Grade 1 and Grade 3).²⁵ The rate is higher in men who have sex with men, particularly those who are HIV infected. Women who are HIV infected also have a higher incidence.²⁶

HPV Vaccine

In the early 1980s, studies confirmed the presence of HPV types 16 and 18 in cervical cancer cells, prompting research and development of a vaccine to prevent HPV. The vaccines that were developed used a new Virus-Like Particle (VLP) technology. VLPs contain particular proteins from the outside layer of the virus but lack the genetic material to actually cause an infection. When injected, VLPs have the ability to produce an immune response due to the presence of foreign material.

Gardasil[®] vaccine was the first FDA-approved HPV vaccine in 2006. It targeted HPV types 6, 11, 16, and 18. Fast-track approval by the FDA, after only a six-month review process, occurred based on data which showed that Gardasil[®] prevented CIN Grades 1, 2, and 3. The FDA approved the vaccine for use in girls and women ages 9 through 26. In 2007, the CDC Advisory Committee on Immunization Practices (ACIP) recommended Gardasil[®] for routine vaccination of girls aged 11 and 12 years and a catch-up schedule for females between the ages of 13 and 26. In October 2009, the FDA approved Gardasil[®] for use in boys and young men ages 9 to 26 for the prevention of genital

warts associated with HPV types 6 and 11.

Cervarix[®], a bivalent recombinant vaccine targeting HPV types 16 and 18, received FDA approval in 2009. It was indicated for females ages 10 through 25 for the prevention of CIN grades 1 to 3, adenocarcinoma in situ, and cervical cancer. The ACIP recommended three doses of Cervarix[®] for routine administration to girls ages 11 or 12, with a catch-up schedule for females ages 13 through 26. In October of 2016, citing low demand for its product, GlaxoSmithKline announced that Cervarix[®] would no longer be marketed in the U.S.

In December 2014, a 9-valent recombinant vaccine (Gardasil[®]9) received FDA approval for use in females ages 9 through 26 for the prevention of genital warts associated with HPV Types 6 and 11 and prevention of anal, cervical, vaginal, and vulvar cancers associated with HPV Types 16, 18, 31, 33, 45, 52, and 58. The FDA also approved Gardasil[®]9 for use in males ages 9 through 15 for prevention of genital warts associated with HPV Types 6 and 11 and prevention of anal cancer associated with HPV Types 16, 18, 31, 33, 45, 52, and 58. In October 2018, the FDA approved expanded use of Gardasil[®]9 to include individuals ages 27 through 45. As of 2016, Gardasil[®]9 is the only marketed HPV vaccine in the U.S.

HPV Vaccine Efficacy

Efficacy results for the HPV vaccine are remarkably consistent among different countries and cultures. Infection rates and disease prevalence have decreased in all countries studied.²⁷ Reductions in disease endpoints are seen within four years of vaccination (even in countries with comparatively low uptake). Even with relatively low levels of population vaccination in the U.S., herd immunity is already occurring (i.e., reduced HPV infection rates even in those unvaccinated). For comparable levels of immunization, immunization at earlier ages confers better population-level effectiveness.

Two extensive, randomized, double-blind trials compared quadrivalent HPV vaccine with placebo among more than 17,000 females aged 15 to 26. After three years, the efficacy of quadrivalent HPV vaccine for preventing CIN 2 or more severe disease due to HPV vaccine types was 97 to 100 percent among HPV-naïve populations and 44 percent among the overall population.²⁸ The efficacy for preventing VIN2 or 3 and VaIN2 or 3 was 100 percent among HPV-naïve populations and 62 percent among the overall population.²⁸ An international randomized trial comparing the 9-valent vaccine with quadrivalent vaccine in approximately 14,000 females aged 16 to 26 found the efficacy of the 9-valent vaccine for

preventing CIN 2 or more severe disease was 97 percent among the HPV-naïve population.²⁹

There appears to be no protective effect against CIN 2/3 or anal cancer in women who have already been infected with HPV 16 and 18 before vaccination. There may be protective effects against the other HPV types contained in the vaccine. HPV vaccination is safe and effective in preventing subsequent infection and cervical disease in older women (ages 27 to 45), but the overall benefit is less than in younger females. In a trial of 5,752 women older than 25 years who were randomly assigned to receive HPV vaccine or placebo, Gardasil[®] was 88 percent effective in the prevention of a combined endpoint of persistent infection, genital warts, vulvar and vaginal precancerous lesions, cervical precancerous lesions, and cervical cancer related to HPV types covered by the vaccine.^{30,31} Efficacy in males was inferred from the female data for the purposes of FDA approval. In those with no prior history of HPV infection, who received three doses of vaccine, vaccine efficacy was 91 percent.

As of 2018, studies have shown that cervical cancer rates have dropped significantly since the introduction of HPV vaccines. Before the HPV vaccines were introduced in 2006, 270,000 women died of cervical cancer worldwide in 2002. As of 2014, the mortality rate from cervical cancer has dropped 50 percent from 1975, due to a combination of HPV vaccination along with an increased focus on cervical screening.

Using data from the New Mexico HPV Pap Registry, after adjustment for changes in cervical screening across the period, reductions in the CIN incidence per 100,000 women screened were significant for all grades of CIN among female individuals 15 to 19 years old after vaccination.³² There was a 9 percent decline in CIN 1, 10.5 percent in CIN 2, and 41.3 percent in CIN 3. Reductions in the CIN 2 incidence were also significant for women 20 to 24 years old (6.3%). The proportion and estimated number of cases of HPV 16/18 positive CIN- 2+ declined from 52.7 percent (1,235 cases) in 2008 to 44.1 percent (819 cases $P < 0.001$).

Cervical disease at age 20 has plummeted in Scotland following a national effort to have girls who are 12 and 13 years old receive a bivalent vaccine against HPV.³³ Compared with a cohort born before the vaccine was available, the vaccinated cohort had nearly a 90 percent reduction in the prevalence of CIN Grade 3 or worse findings on their cervical smears at age 20. The prevalence was 0.59 percent among the unvaccinated versus 0.06 percent among the vaccinated. Similar drops were also noted for the lower CIN grades.

HPV Vaccine Safety

The three HPV vaccines have documented safety in large clinical trials, and extensive post-licensure data. They all use VLPs, which mimic the viral capsid, do not contain genetic material, and are produced in biologic systems, which have well-established safety records. The most common adverse event is injection site reaction. Between June 2006 and March 2013, approximately 57 million doses of quadrivalent HPV vaccines were distributed in the U.S. and during that time period the U.S. Vaccine Adverse Event Reporting System (VAERS) received 21,194 reports of adverse events following HPV immunization among females. The vast majority (92 percent) were considered mild.³⁴ Among serious events, headache, nausea, vomiting, fatigue, dizziness, syncope, and generalized weakness were the most frequently reported.³⁵

In terms of population-level safety, no new safety problems have been identified. There has been no increased risk of Guillain-Barré Syndrome compared with other vaccines in similar age groups. In accidentally vaccinated pregnant women, the rates and types of birth defects in exposed pregnancies is the same as the rate in unexposed pregnancies. There has been no association between vaccination and development or exacerbation of autoimmune diseases.

Vaccine Recommendations

The ACIP recommends that boys and girls should routinely be vaccinated at 11 or 12 years of age with the two-dose regimen, except when immunocompromised and then the three-dose regimen should be used (Exhibit 4).³⁶ The vaccination series can be started at age 9. The “catch-up” vaccine schedule is a three-dose series for females above age 15 through age 26 and males above 15 years of age to 21 years of age not previously vaccinated with HPV vaccine. The recommended vaccination schedule is supported by the American Academy of Pediatrics, American Academy of Family Physicians, and the American College of Obstetricians and Gynecologists.

The FDA labeled indication for Gardasil[®]9 now includes those up to age 45. The ACIP is evaluating

whether to expand their current HPV vaccine recommendation to include this new age group. Cost data presented at the October 2018 ACIP meeting, though incomplete, showed that increasing use recommendations of 9-valent vaccine is not likely to be cost effective.³⁷ In addition, preliminary data showed that receiving the vaccine would not likely have a significant positive impact on those who may have chronic HPV infections that go on to become HPV-associated cancers. A permissive use recommendation from the ACIP in 2019 for those ages 27 to 45 is more likely than a routine use recommendation.³⁸ This issue is supposed to be addressed at the June 2019 ACIP meeting.³⁹

HPV Vaccination Rates in the U.S.

Unfortunately, the U.S. has a relatively low rate of HPV vaccination compared to other childhood vaccines (Exhibit 5).⁴⁰ As of 2017, 48.6 percent of 13 to 17 year-olds have been vaccinated; this rate has increased from 33.4 percent in 2015. In the U.S., because of our low HPV immunization rate, approximately 2,500 women are condemned each year to die of preventable cervical cancers. This number of deaths is equivalent to one 747 jetliner crash every three months. It is estimated that by increasing complete-dose HPV vaccination coverage (to 80 percent in females), approximately 53,000 additional cases of cervical cancer could be prevented in the U.S. over the lifetimes of those females currently less than 12 years old.⁴¹

Strategies to Increase Vaccination Rates

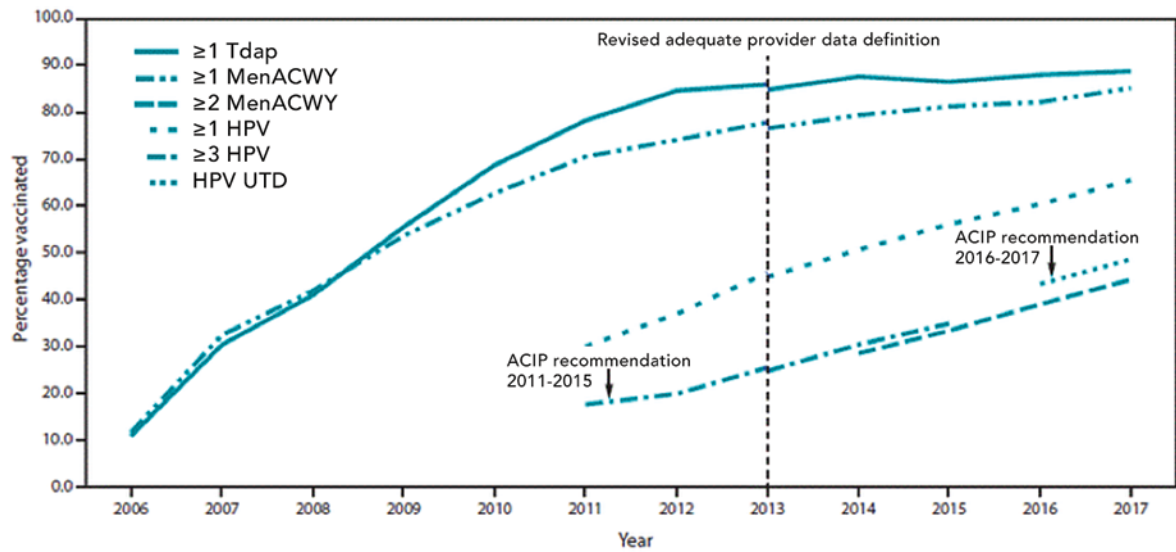
There are many reasons why parents do not vaccinate their children against HPV and other diseases. The top five reasons for not getting the HPV vaccine are shown in Exhibit 6.⁴² Providers may not give or recommend HPV vaccination for various reasons, including lack of urgency, burnout, finances, or too many other issues to deal with in a routine visit. In one survey, white parents rated vaccines less important in preventing some illnesses than did non-white ($P \leq 0.006$ for meningitis, hepatitis, HPV, influenza and rotavirus) and rated the number of injections per visit more important than the number of diseases prevented (51.6% white versus 34.2% non-white; $P 0.002$).⁴³ In this survey, providers underestimated parental attitudes toward vaccine importance (particularly influenza and HPV).⁴³

Many clinicians may feel that face-to-face education is the best way to increase vaccination rates. A Cochrane review found that there is limited, low-quality evidence that suggests that face-to-face interventions to inform or educate parents about

Exhibit 4: HPV Vaccination Regimen and Schedule³⁶

Age	Regimen	Schedule
9 through 14 years	2-dose	0, 6 to 12 months
15 through 26 years or immunocompromised at any age	3-dose	0, 2, 6 months

Exhibit 5: Estimated Coverage with Selected Vaccines and Doses Among Adolescents Aged 13-17 Years, by survey year and ACIP recommendations National Immunization Survey-Teen, United States, 2006-2017⁴⁰



UTD: up to date

childhood vaccination have little or no impact on immunization status, knowledge, or understanding of vaccination.⁴⁴ Crafting good messages about vaccination also does not always work. One messaging trial found that pro-vaccine messages do not always work as intended.⁴⁵ In this trial, which was trying to increase MMR vaccination, parents who were shown images of sick children had increased expressed belief in a vaccine/autism link and a dramatic narrative about an infant in danger increased self-reported belief in serious vaccine side effects. Therefore, emphasizing the cancer risk of HPV may not work to increase rates.

Overall, there is a great deal of research on the knowledge, attitudes, and beliefs of parents about vaccination, but there is little research on what communication techniques actually change the behavior of parents. The focus has been on ‘what’

people think more than ‘how’ people think. Also, our core communication assumptions are often wrong. Many clinicians believe that if only the parents understood the facts they would realize they were making the wrong choice. This is the Information Deficit Model. Unfortunately, vaccination decisions are based on emotion, and not on logic, reason, or facts.

Correcting knowledge gaps is often not enough to address parents who have concerns about vaccines. Clinicians and managed care need interventions based on how people actually think, rather than how they ought to think. Four evidence-based strategies to improve vaccine communication are “strong” recommendations, presumptive recommendations, blanket recommendations, and motivational interviewing. The first three are for use with accepting parents or patients, and the last is for resistant individuals.

Exhibit 6: Top Five Reasons for Not Vaccinating Adolescents with HPV Vaccine⁴²

Parents of Girls		Parents of Boys	
Reason	Percent	Reason	Percent
Lack of Knowledge	15.5	Not recommended	22.8
Not needed or necessary	14.7	Not needed or necessary	17.9
Safety concern/Side effects	14.2	Lack of knowledge	15.5
Not recommended	13	Not sexually active	7.7
Not sexually active	11.3	Safety concern/Side effects	6.9

A strong HPV vaccine recommendation should be given to everyone eligible, and the vaccine should be given on the same day as the discussion. Clinicians should use unequivocal language that demonstrates support and give the same weight to HPV as other vaccines (which is a blanket recommendation). With a blanket recommendation, the clinician recommends HPV the same way as they would recommend other adolescent vaccines. For example, “Your child needs three shots today: HPV vaccine, meningococcal vaccine and Tdap vaccine.”

In one trial, the best predictor of vaccination uptake, for both hesitant and non-hesitant parents, was how the provider started the conversation.⁴⁶ A participatory start to the vaccine conversation linguistically provides parents with more decision-making latitude — “Have you thought about what shots you’d like to get today?” Presumptive language or recommendation presupposes that parents will get the vaccine(s). Examples include “Well, we have some shots to do today” or “Susie is due for three shots today.” The presumptive style works because the presumptive tone is perceived as the socially acceptable norm. Parents perceive vaccination decisions as complicated and humans use the “status quo bias” (also called a default bias) for complicated decisions, meaning we go with what is expected or ‘normal.’

Presumptive recommendations work to increase HPV vaccination rates. In a randomized, controlled trial in 29 clinics which compared announcements

(presumptive recommendation), conversations about the vaccine, and usual care to bring up the topic of HPV vaccine, announcements produced a 5.4 percent increase in vaccination rates over usual care.⁴⁷ There was no difference between conversations and usual care.

For the reluctant parent/patient, when a strong presumptive blanket recommendation does not work, the clinician should pivot to motivational interviewing, which is a way of reorienting the relationship with patients. The clinician’s focus is being a “helper” in the change process rather than reaching a goal. It works by leveraging a person’s intrinsic motivation for a behavior. The four tenants of motivational interviewing are empathy, collaboration, evocation, and support for autonomy.

A cluster randomized controlled trial among 16 public and private practices in Colorado with over 30,000 adolescents evaluated motivational interviewing as part of a HPV vaccination strategy. The trial utilized a multi-component intervention of a HPV fact sheet developed by patients and providers, HPV decision aid, tailored web-based intervention, and clinician communication training. The training taught clinicians how to give strong, blanket, presumptive recommendations and use motivational interviewing in those reluctant to vaccinate. Adolescents in the intervention practices had significantly higher odds of HPV vaccine series initiation and completion than those in the control practices.⁴⁸

Exhibit 7: Cost-Effectiveness Ratios for HPV Vaccination Strategies⁴⁹

Vaccine evaluated (vs. no vaccination unless noted)	Cost per QALY gained
Adolescent females (2vHPV or 4vHPV)	\$5,000 to \$30,000
Adolescent males (4vHPV), vs. female-only	\$25,000 to \$45,000 (favorable scenario) \$85,000 to >\$250,000 (unfavorable scenario)
MSM through age 26 years	< \$50,000
9vHPV (vs. 4vHPV)	< \$0 (cost-saving)
2-dose 9vHPV (vs. 3-dose 9vHPV)	< \$0 (cost-saving)
QALY = quality-adjusted life year 2vHPV = bivalent HPV vaccine 4vHPV = quadrivalent HPV vaccine	9vHPV = nonavalent HPV vaccine MSM = men who have sex with other men
For adolescent males, in the “favorable scenario,” female vaccination coverage is lower (e.g., 20%) and all potential health benefits are included in the analysis. In the “unfavorable scenario,” female vaccination coverage is higher (e.g., 75%) and only the health outcomes for which the vaccine is indicated are included in the analysis.	

In addition to getting the first shot in the HPV series, it is important for the patient to complete the series. This is easier now with the two-dose regimen for most patients. Some ways to improve completion include persistent reminders, making access easy by automatically scheduling the second dose at the first dose visit, screening for vaccination needs at every visit, and making sure to emphasize the need for all doses when giving the first.

Clinicians should also engage adolescents to help them ensure adequate immunization. Adolescence is a time for increasing responsibility for self-care, but adolescents probably cannot self-consent for vaccination. All states have laws pertaining to sexually transmitted disease treatment and/or prevention and sexual health, and they are all different. Most states are silent on the issue of whether “prevention” through vaccination is an allowable scenario. However, even in states that allow this, cost and confidentiality can still be a concern.

Clinicians can empower adolescents to help ensure they get adequate vaccinations. They should start prepping adolescents early to be self-advocates. Vaccine discussions can occur with the parents and the adolescent, but clinicians should support the one advocating for vaccines. Practices can have teen friendly resources and strategies available, including teen friendly reminders. For supportive teens, have them encourage their friends to get vaccinated.

Economics

When launched, the HPV vaccine was the most expensive vaccine up to that time. Because of the potential use in a large segment of the population, payers had some level of concern about the cost impact of HPV vaccination. However, the efficacy data on these vaccines resulted in rapid coverage policies at most plans.

As shown in Exhibit 7, the current recommendations for HPV vaccine use are considered cost effective.⁴⁹ The ACIP is currently evaluating the cost-effectiveness of expanding the age range for HPV vaccine recommendations up to age 45, using five economic models. All five of the models are dynamic (include “herd effects”), include a wide range of health outcomes (cervical precancers and cancer, other HPV-associated cancers, and genital warts), apply updated direct medical costs estimates for HPV-associated cancers, exclude productivity costs, and examine a long time horizon (~100 years or more). It does not appear to be cost effective to expand the recommendations for HPV vaccine to those over the age of 26.⁵⁰

Payer Strategies

In a survey of high-performing health plans on the Health Effectiveness Data and Information Set (HEDIS[®]) HPV vaccine for female adolescents’ measure, the plans used multiple strategies that support HPV vaccination, particularly the “normalizing” of the vaccine. The plans efforts highlighted patient and provider education, reminders, feedback loops, community collaborations, immunization registries and use of medical home concepts — including team-driven efforts and coordination.⁵¹ In addition, health plans can work to eliminate financial barriers to access and coverage. Overall, health plans can employ multiple efforts to encourage vaccination by implementing activities that involve the patient, provider and community.

Conclusion

HPV infection is common in both men and women, with acute infection often mild and transient. The long-term consequences are now well known and include an increased risk of several cancer types. Vaccination against the oncogenic strains can prevent cancer. HPV vaccines have been available in the U.S. since 2006. Despite availability for more than a decade, rates of immunization in the U.S. remain suboptimal. There is good evidence that HPV vaccines are capable of preventing cervical cancers and other HPV-related illnesses. HPV vaccines (especially for younger ages) are considered cost-effective. Recently, the age for potential immunization for HPV has been extended to age 45. To facilitate vaccination, clinicians should start with strong, presumptive, blanket recommendations for HPV vaccine, along with any other vaccines due at a visit. When there is resistance, the clinician should switch to more nuanced, less confrontational techniques. Payers need to develop effective strategies to improve HPV vaccination rates — especially in younger age groups where there is higher cost-effectiveness.

Author Bios

Kenneth A. Alexander, MD, PhD is Chief of the Division of Infectious Diseases at the Nemours Children’s Hospital and is a Professor of Pediatrics at The University of Central Florida College of Medicine in Orlando, FL.

Amanda F. Dempsey, MD, PhD, MPH is an Associate Professor of Pediatrics at the University of Colorado Denver Children’s Outcomes Research Program and a Primary Care Pediatrician at Children’s Hospital Colorado in Aurora, CO.

Gary M Owens, MD is President of Gary Owens and Associates in Ocean View, DE.

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