

# Protecting Women Against Human Papillomavirus: Benefits, Barriers, and Evidence-Based Strategies to Increase Vaccine Uptake

Tamera Coyne-Beasley, Bridget E. Hochwalt

**Human papillomavirus (HPV) infection significantly impacts women, as it can cause cancers and precancers of the cervix, vulva, vagina, oropharynx, and anus. However, many of these cancers can be prevented by HPV vaccination. Despite evidence of vaccine effectiveness and safety, vaccination rates remain low. Evidence-based strategies should be utilized to reduce barriers and increase vaccination rates.**

**H**uman papillomavirus (HPV) is the most common sexually transmitted infection in the United States. Approximately 85% of sexually active women and 91% of sexually active men will be infected with HPV in their lifetime [1]. Approximately half of new infections occur among individuals aged 15–24 years [2]. Though genital skin contact is the primary mode of transmission, the infection does not require sexual penetration [3]. The most common symptom of HPV infection is genital warts, although many infected people are asymptomatic, and the virus often resolves on its own. Physicians diagnosed over 400,000 cases of genital warts in 2013 [4]. However, the most serious consequence of HPV infection is cancer.

HPV infection is known to cause cervical, vulvar, and vaginal cancer in women and penile cancer in men. It is also an attributable cause of anal and oropharyngeal cancer in both men and women. Between 1993 and 2005, HPV was linked to 90.6% of all cervical cancer cases, 70.1% of oropharyngeal cancers, and 91.1% of anal cancers in the United States [5].

HPV-related cancers disproportionately affect women in the United States. There are 17,600 women affected by HPV-related cancers annually; of those, approximately 11,000 are cervical cancer diagnoses [5]. In comparison, 9,300 men are affected by HPV-attributable cancer each year [5]. Women also have a higher prevalence of anal cancer than men (2,600 cases versus 1,400 cases annually). However, men have a higher prevalence of oropharyngeal cancer than women (7,200 cases versus 1,800 cases annually) [5]. Among women, the incidence of cervical cancer disproportionately affects African Americans and Latinas, who are more likely to be diagnosed with cervical cancer and have higher

cervical cancer mortality rates than whites (see Table 1). Delayed diagnosis is a major contributor to this disparity [6]. White women have higher rates of HPV-associated anal and vulvar cancer than black and Latina women [6].

The first HPV vaccine available in the United States, the quadrivalent HPV vaccine (4vHPV), was licensed in 2006 for females aged 9–26 years, although administration was routinely recommended at ages 11–12 years (prior to the onset of sexual activity for most adolescents) [7]. 4vHPV was approved for males permissively in 2009 for genital wart prevention and was recommended routinely for males in 2011, at which time 4vHPV was licensed by the US Food and Drug Administration for the prevention of anal cancer in both males and females [8]. The bivalent HPV vaccine (2vHPV) for cervical cancer prevention and the nonavalent HPV vaccine (9vHPV) were introduced in 2009 and 2014, respectively [7]. Despite evidence of efficacy and safety for all of the HPV vaccines, vaccination rates continue to lag behind all other vaccines recommended for adolescents [9]. This commentary will highlight the benefits of vaccination, factors that influence vaccination rates, evidence-based strategies for increasing uptake, and current US vaccine recommendations.

**TABLE 1.**  
**Incidence and Mortality Rates of Cervical Cancer by Race/Ethnicity**

	Incidence rate (per 100,000 women)	Mortality rate (per 100,000 women)
African American or black	8.9	3.9
Hispanic	9.4	2.6
Caucasian or white	7.5	2.1

Source: National Cancer Institute [6].

Electronically published November 16, 2016.

Address correspondence to Dr. Tamera Coyne-Beasley, University of North Carolina at Chapel Hill, CB #7225, 231 MacNider, Chapel Hill, NC 27599 (tamera\_coyne-beasley@med.unc.edu).

**NC Med J. 2016;77(6):402-405.** ©2016 by the North Carolina Institute of Medicine and The Duke Endowment. All rights reserved. 0029-2559/2016/77610

## Benefits of HPV Vaccination

4vHPV protects against the non-oncogenic types 6 and 11, which cause 90% of genital warts [10], and the oncogenic types 16 and 18, which cause approximately 66% of cervical cancer [5]. 9vHPV protects against another 5 oncogenic types (31, 33, 45, 52, and 58) that collectively cause approximately 80% of HPV-attributable cervical cancers in the United States [5]. Both 4vHPV and 9vHPV are licensed to prevent vaginal, vulvar, and anal cancers.

The incidence of HPV infection among female adolescents has decreased since the vaccine was introduced. The total US prevalence of the 4vHPV infection types (6, 11, 16, and 18) among female adolescents aged 14–19 years has decreased significantly—from 11.5% in the pre-vaccination era (2003–2006) to 4.3% in the post-vaccination era (2009–2012); among females aged 20–24 years, rates have decreased from 18.5% to 12.1% [11]. Among females aged 14–24 years who received the 4vHPV vaccine, the prevalence rate of the 4 HPV types was only 2.1%, compared with 16.9% among females who did not receive the vaccine [11].

HPV vaccination also prevents precancerous lesions. Pap tests detect cervical intraepithelial neoplasia (CIN) grade 2/3, which is a precancerous lesion of the cervix caused by the HPV infection. If left untreated, these lesions may evolve into cancer. Women who test positive may undergo follow-up tests such as a repeat Pap test, colonoscopy, loop electrosurgical excision procedure (LEEP), and/or conization. These tests can be uncomfortable and can weaken the cervix, potentially leading to later obstetric complications such as premature delivery and low infant birth weight [12]. Pap tests that show false-positive results for CIN 2/3 can cause undue psychological stress, repeat testing, and physical risk on healthy patients.

By preventing cervical cancer, the HPV vaccine is projected to save the United States billions of dollars in annual health care costs related to cervical cancer screening and cancer treatments. Cervical cancer screening and follow-up procedures cost the nation approximately \$6.6 billion per year, which accounts for more than 80% of the total costs for preventing and treating HPV-attributable diseases. Comparatively, cancer treatments account for 12% of total HPV-attributed health care costs [13].

Research has demonstrated that the HPV vaccine is highly effective in preventing HPV infections, cancers, and precancerous lesions [14, 15]. Side effects of the vaccine most commonly include injection site reactions such as pain, erythema, and swelling [16]. The vaccine has not been demonstrated to be an attributable cause of neurodegenerative disorders including Guillain-Barré Syndrome [17]. The vaccine is contraindicated in individuals with hypersensitivity, including those who have severe allergic reactions to yeast (a vaccine component) or those who had a severe reaction after a previous dose of HPV vaccine [16].

## HPV Vaccination Uptake and Disparities

National estimates suggest that 53,000 lifetime cervical cancer cases will be prevented for girls currently age 12 years and younger if the Healthy People 2020 goal of 80% vaccine coverage is met [18]. While HPV vaccination uptake rose modestly from 2014–2015, it remains low in comparison to other recommended vaccines. In 2015, 60% of females aged 13–17 years had received at least 1 dose of the HPV vaccine, although only 39.7% had received 3 or more doses. Rates for receiving the initial dose (41.7%) and for completing the series (21.6%) were lower among males in the same age group. By comparison, 87.6% of 13–17-year-old adolescents had received the Tdap vaccine, and 79.3% had received 1 or more meningococcal vaccine. North Carolina had a higher rate of HPV vaccination initiation (65.7%) for females than the US average, although rates for receiving 3 or more doses among females and rates for males are on par with the US average [9].

In the United States, Latina (68.4%) and African American (66.9%) females aged 13–17 years have higher HPV vaccination initiation rates than white females (59.2%). However, Latina females (46.2%) are more likely to have 3 or more doses than are African American (40.8%) and white (39.6%) females [9]. In younger children (aged 9–14 years), the immunogenicity of 2 doses separated by 6–12 months is higher than the immunogenicity of 3 doses for 15–26-year-olds.

The National Health and Nutrition Examination Survey found that only 32.6% of females aged 20–24 years and 14.7% of females aged 24–29 years had received 1 or more HPV vaccine doses in the 2009–2012 survey collection period. This compares to 51.4% of females aged 14–19 years who received the vaccine in the same time frame [11]. Females up to age 26 years should receive the vaccine if they did not receive it when they were younger.

Adolescents living in poverty were also more likely to initiate and complete the HPV vaccine [9]. This may be because the vaccination is free for uninsured, underinsured, and other qualifying low-income adolescents up to age 18 years through the Vaccines for Children Program.

## Barriers to Uptake

A number of barriers contribute to the low uptake of HPV vaccination (see Table 2). For many parents, concerns about vaccination encouraging adolescents' earlier sexual debut and greater promiscuity are a barrier [20, 21]. Despite these fears, research shows that adolescents who received the vaccine have not had greater numbers of sexual partners than those who did not receive the vaccine [11]. Additional barriers are low perceived risk of HPV infection and lack of knowledge about HPV and the vaccine [22]. Parents also remain concerned about safety [23, 24] and effectiveness [24].

Physician recommendation is one of the most influential factors in vaccine uptake. However, studies have demon-

strated that some providers do not consistently or strongly recommend the vaccine to all eligible adolescents at ages 11–12 years [22]. Physician hesitancy may be due to an overestimation of parental objection, and physicians may not offer a strong recommendation when faced with parental reluctance [25].

Accessibility and missed opportunities are additional barriers to vaccination of adolescents. Adolescents visit physician offices less frequently than do younger children, and they are more likely to come for an acute visit, when the vaccine is less likely to be recommended than during a routine exam. This is a missed opportunity, and HPV vaccination should be offered to all eligible adolescents and young adults at all visits. Cost can also impact vaccination access [20]. However, under the Patient Protection and Affordable Care Act of 2010 and the Vaccines for Children Program, all age-eligible females and males—including those who are uninsured—should have coverage for this vaccine. Some private insurance companies may require copayments.

### Evidence-Based Strategies to Increase Vaccine Initiation and Completion

Several evidence-based strategies to increase vaccine initiation and completion have been endorsed by the Centers for Disease Control and Prevention, the National Vaccine Advisory Committee, and the Advisory Committee on Immunization Practices (ACIP). One of these strategies is the Assessment, Feedback, Incentives, and eXchange (AFIX) approach. With AFIX, the state immunization branch or another external source assesses a physician’s practice to evaluate vaccination coverage for specific groups and to determine strategies for improvement. Practices are then given feedback about the results of their assessment. Various incentives are used to build morale. Incentives may involve new community partnerships and opportunities for collaboration, which can lead to sharing of information and ideas across practices [26]. This strategy has been successful in North Carolina [27].

**TABLE 2.**  
**Barriers to Human Papillomavirus Vaccine Uptake**

Barriers
Lack of physician recommendation or lack of strong recommendation [22, 25]
Physician hesitancy [25]
Parental perception that recommended vaccination age (11–12 years) is too young [19]
Parents belief that vaccination would encourage early sexual debut [20, 21, 24]
Parental low perceived risk of HPV infection [22]
Parental lack of knowledge about HPV and/or HPV vaccine [22, 23]
Concerns about vaccine safety [21, 23, 24]
Concerns about vaccine effectiveness [24]
Cost of vaccine [20]
Mistrust of health care provider recommendation [20]

Note. HPV, human papillomavirus.

Other strategies include immunization information systems, parent recommendation and reinforcement, reminders and recall directed at providers, and reminders and recall directed at patients. Matheson and colleagues found that text-message reminders effectively increased the likelihood of adolescents receiving their second and third doses of vaccine on time [28]. Other studies have found that calls, letters, and e-mails were effective in increasing initiation and completion of HPV vaccination [29]. A combination of patient/parent reminders and physician messaging and reminders has been used to increase adolescent uptake. Notably, physician-directed reminders may be most effective for initiating the vaccine series, while parent/patient reminders can be especially useful for increasing series completion [29].

### Current Recommendations

The ACIP recommends that routine HPV vaccination be initiated at age 11 or 12 years in females and males, before most adolescents’ sexual debut. The immunogenicity of the vaccine (its ability to mount an immune response) is also greatest in the younger age group [8]. However, the vaccine is recommended beginning at age 9 years for children with any history of sexual abuse or assault who have not initiated or completed the series [15]. Vaccination is also recommended for females aged 13–26 years and for males aged 13–21 years who have not been previously vaccinated or who have not completed the series. Males aged 22–26 years may be vaccinated. For men who have sex with men, ACIP recommends routine HPV vaccination as for all males, and vaccination is recommended through age 26 years for those who were not adequately vaccinated previously.

The vaccine should be given even if the age-eligible young person has engaged in sexual activity, as an individual is unlikely to have contracted all the HPV types in the vaccine. They will receive protection from any types to which they have not been exposed. Vaccination of females is recommended with the 2vHPV, 4vHPV (if available), or 9vHPV vaccine. Vaccination of males is recommended with 4vHPV or 9vHPV. In October 2016, the ACIP changed dosing recommendations from a 3-dose series to a 2-dose series for adolescents initiating the series between ages 9–14 years due to higher immune response to the vaccine in this age group. Doses should be delivered 6–12 months apart. Adolescents initiating the series between ages 15–26 years continue to need the 3-dose series, which can be administered at 0, 1–2, and 6 months [30]. If the vaccine schedule is interrupted, the vaccination series does not need to be restarted [8].

### Conclusion

HPV infection poses a significant burden on women, as it can cause genital warts and cervical, anal, oropharyngeal, vulvar, and vaginal cancer and precancer. The need for invasive cervical procedures to diagnose or treat cervical can-

cer can subsequently lead to premature birth and low infant birth weight. Fortunately, most genital warts and the majority of HPV-associated cancers can be prevented by HPV vaccination. However, the vaccine is not currently licensed for the prevention of penile or oropharyngeal cancers. Men and women can be vaccinated at ages 9–26 years, although the vaccine is routinely recommended at ages 11–12 years. Despite evidence of effectiveness, rates of HPV vaccination initiation and completion remain low. Greater implementation and further development of evidence-based strategies are needed to reduce HPV disease and eliminate HPV disparities in the United States. *NCMJ*

**Tamera Coyne-Beasley, MD, MPH, FAAP, FSAHM** professor, Department of Pediatrics, Division of General Pediatrics and Adolescent Medicine, University of North Carolina at Chapel Hill; director, NC Child Health Research Network, Chapel Hill, North Carolina.

**Bridget E. Hochwalt, BA** research assistant, Department of Pediatrics, Division of General Pediatrics and Adolescent Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

### Acknowledgments

Potential conflicts of interest. T.C.-B. and B.E.H. have no relevant conflicts of interest.

### References

- Chesson HW, Dunne EF, Hariri S, Markowitz LE. The estimated lifetime probability of acquiring human papillomavirus in the United States. *Sex Transm Dis.* 2014;41(11):660-664.
- Satterwhite CL, Torrone E, Meites E, et al. Sexually transmitted infections among US women and men: prevalence and incidence estimates, 2008. *Sex Transm Dis.* 2013;40(3):187-193.
- Burchell AN, Winer RL, de Sanjosé S, Franco EL. Chapter 6: Epidemiology and transmission dynamics of genital HPV infection. *Vaccine.* 2006;24(Suppl 3):S52-S61.
- Centers for Disease Control and Prevention (CDC). Figure 49. Genital Warts—Initial Visits to Physicians' Offices, United States, 1966–2013. CDC website. <http://www.cdc.gov/std/stats13/figures/49.htm>. Last reviewed December 16, 2014. Accessed November 8, 2016.
- Saraiya M, Unger ER, Thompson TD, et al; HPV Typing of Cancers Workgroup. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. *J Natl Cancer Inst.* 2015;107(6):djv086.
- National Cancer Institute. SEER Stat Fact Sheets: Cervix uteri cancer. National Cancer Institute: Surveillance, Epidemiology, and End Results Program website. <http://seer.cancer.gov/statfacts/html/cervix.html>. Accessed October 24, 2016.
- Petrosky E, Bocchini JA Jr, Hariri S, et al; Centers for Disease Control and Prevention (CDC). Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep.* 2015;64(11):300-304.
- Centers for Disease Control and Prevention (CDC). Recommendations on the use of quadrivalent human papillomavirus vaccine in males—Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR Morb Mortal Wkly Rep.* 2011;60(50):1705-1708.
- Reagan-Steiner S, Yankey D, Jeyarajah J, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13–17 years—United States, 2015. *MMWR Morb Mortal Wkly Rep.* 2016;65(33):850-858.
- Koutsky LA, Ault KA, Wheeler CM, et al; Proof of Principle Study Investigators. A controlled trial of a human papillomavirus type 16 vaccine. *N Engl J Med.* 2002;347(21):1645-1651.
- Markowitz LE, Liu G, Hariri S, Steinau M, Dunne EF, Unger ER. Prevalence of HPV after introduction of the vaccination program in the United States. *Pediatrics.* 2016;137(3):e20151968.
- Sadler L, Saftlas A, Wang W, Exeter M, Whittaker J, McCowan L. Treatment for cervical intraepithelial neoplasia and risk of preterm delivery. *JAMA.* 2004;291(17):2100-2106.
- Chesson HW, Ekwueme DU, Saraiya M, Watson M, Lowy DR, Markowitz LE. Estimates of the annual direct medical costs of the prevention and treatment of disease associated with human papillomavirus in the United States. *Vaccine.* 2012;30(42):6016-6019.
- Paavonen J, Naud P, Salmerón J, et al; HPV PATRICIA Study Group. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet.* 2009;374(9686):301-314.
- Markowitz LE, Dunne EF, Saraiya M, et al; Centers for Disease Control and Prevention (CDC). Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2014;63(RR-05):1-30.
- Gardasil 9 [package insert]. Whitehouse Station, NJ: Merck & Co; 2014. [https://www.merck.com/product/usa/pi\\_circulars/g/gardasil\\_9/gardasil\\_9\\_pi.pdf](https://www.merck.com/product/usa/pi_circulars/g/gardasil_9/gardasil_9_pi.pdf). Accessed July 18, 2016.
- Gee J, Naleway A, Shui I, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. *Vaccine.* 2011;29(46):8279-8284.
- Chesson HW, Ekwueme DU, Saraiya M, Dunne EF, Markowitz LE. The estimated impact of human papillomavirus vaccine coverage on the lifetime cervical cancer burden among girls currently aged 12 years and younger in the United States. *Sex Transm Dis.* 2014;41(11):656-659.
- Hull PC, Williams EA, Khabele D, Dean C, Bond B, Sanderson M. HPV vaccine use among African American girls: qualitative formative research using a participatory social marketing approach. *Gynecol Oncol.* 2014;132(Suppl 1):S13-S20.
- Allen JD, Othus MK, Shelton RC, et al. Parental decision making about the HPV vaccine. *Cancer Epidemiol Biomarkers Prev.* 2010;19(9):2187-2198.
- Brawner BM, Baker JL, Voytek CD, et al. The development of a culturally relevant, theoretically driven HPV prevention intervention for urban adolescent females and their parents/guardians. *Health Promot Pract.* 2013;14(4):624-636.
- Stokley S, Jeyarajah J, Yankey D, et al; Immunization Services Division, National Center for Immunization and Respiratory Diseases, CDC; Centers for Disease Control and Prevention (CDC). Human papillomavirus vaccination coverage among adolescents, 2007–2013, and postlicensure vaccine safety monitoring, 2006–2014—United States. *MMWR Morb Mortal Wkly Rep.* 2014;63(29):620-624.
- Allen JD, de Jesus M, Mars D, Tom L, Cloutier L, Shelton RC. Decision-making about the HPV vaccine among ethnically diverse parents: implications for health communications. *J Oncol.* 2012;2012:401979.
- Dorell C, Yankey D, Jeyarajah J, et al. Delay and refusal of human papillomavirus vaccine for girls, national immunization survey-teen, 2010. *Clin Pediatr (Phila).* 2014;53(3):261-269.
- Hughes CC, Jones AL, Feemster KA, Fiks AG. HPV vaccine decision making in pediatric primary care: a semi-structured interview study. *BMC Pediatr.* 2011;11:74.
- Centers for Disease Control and Prevention (CDC). Immunization strategies for healthcare practices and providers. CDC website. <http://www.cdc.gov/vaccines/pubs/pinkbook/strat.html>. Updated May 15, 2015. Accessed July 13, 2016.
- Gilkey MB, Dayton AM, Moss JL, et al. Increasing provision of adolescent vaccines in primary care: a randomized controlled trial. *Pediatrics.* 2014;134(2):e346-e353.
- Matheson EC, Derouin A, Gagliano M, Thompson JA, Blood-Siegfried J. Increasing HPV vaccination series completion rates via text message reminders. *J Pediatr Health Care.* 2014;28(4):e35-e39.
- Walling EB, Benzoni N, Dornfeld J, et al. Interventions to improve HPV vaccine uptake: a systematic review. *Pediatrics.* 2016;138(1).
- Centers for Disease Control and Prevention (CDC). CDC recommends only two HPV shots for younger adolescents. CDC website. <http://www.cdc.gov/media/releases/2016/p1020-hpv-shots.html>. Updated October 20, 2016. Accessed November 8, 2016.