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Human Papillomavirus Vaccination

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Abstract

A 24-year-old woman is being seen for routine health care. She has not received any vaccinations against human papillomavirus (HPV). The patient initiated sexual activity at 18 years of age and has had three male sex partners. What would you recommend regarding HPV vaccination?

THE CLINICAL PROBLEM

Genital HPV infection is the most common sexually transmitted infection in the United States.[1] Infection occurs in epithelial tissue, and transmission is generally by means of sexual contact. Most HPV infections are not noticed; more than 90% of new infections clear or become undetectable within 1 to 2 years. Persistent infection with some HPV types can progress over a period of years to cervical cancer as well as to other anogenital cancers, including cancers of the vagina, vulva, penis, and anus, and to cancer of the oropharynx.[2] The natural history of cervical HPV infection has been well described (Fig. 1). First HPV infection often occurs around the age that sexual encounters begin, with cervical precancers detected later, depending on the patient's age at cervical cancer screening. Cervical cancer is usually diagnosed decades after infection.[3]

More than 200 different HPV types have been identified, including approximately 40 types that infect mucosal epithelium.[4] Twelve types have been defined as oncogenic (or high-risk), and 8 to 12 types as probably or possibly oncogenic. The HPV16 type has the highest risk of progression to cancer. Almost all cervical cancers are attributable to HPV. Worldwide, HPV16 and HPV18 are responsible for approximately 70% of cervical cancers and for an even greater percentage of other HPV-attributable cancers (i.e., those that are probably caused by HPV).[2] HPV6 and HPV11, which are not classified as oncogenic, cause almost all cases of anogenital warts and recurrent respiratory papillomatosis.[5]

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In the United States, an estimated 42 million persons are infected with a disease-causing genital HPV type, with approximately 13 million persons being newly infected each year.[1] Data from U.S. cancer registries are used to determine the annual number of HPV-associated cancers, which are defined as primary epithelial cancers at anogenital and oropharyngeal sites. Estimates of HPV-attributable cancers come from studies that detect and type the virus in cancer tissue.[6] An estimated 37,300 new cases of HPV-attributable cancers occurred annually during the 2015–2019 period in the United States (Table 1).

In the United States, the most common HPV-attributable cancers are cervical cancers (approximately 11,100 cases per year) and oropharyngeal cancers (approximately 14,800 cases per year, most of which occur in men). The incidence of cervical cancer has been decreasing in the United States over the past several decades as a result of early detection and treatment of precancers during screening and follow-up, whereas the incidence of oropharyngeal cancer has been increasing.[8] In the United States, there are ethnic and racial disparities in HPV-associated cancers that vary according to cancer. For example, rates of cervical cancer are highest among Black and Hispanic women, whereas rates of oropharyngeal cancer are highest among White men.

Worldwide, an estimated 690,000 cancers are attributable to HPV each year, with cervical cancer being the most common.[9] The majority of cases of cervical cancer and related deaths occur in low- and middle-income countries, where screening for cervical cancer is not widely available. Highly effective prophylactic HPV vaccines can prevent HPV infection and decrease the burden of disease due to HPV.

STRATEGIES AND EVIDENCE

CLINICAL PRESENTATION

HPV infection is usually asymptomatic. No treatment is available for asymptomatic HPV infection; treatment is directed at HPV-associated conditions.[10] Anogenital warts, which appear as flat, papular, or cauliflower-like growths, are usually diagnosed on the basis of clinical inspection. Recurrent respiratory papillomatosis, a rare condition, usually manifests as hoarseness and stridor and requires referral to an otolaryn-gologist. Most genital HPV infections are diagnosed on the basis of HPV testing as part of screening for cervical cancer. Several professional organizations provide guidelines regarding cervical cancer screening with cytologic testing, HPV tests, or a combination of these.[11] Detailed discussion of screening methods is beyond the scope of this article. There is consensus that screening should not start before 21 years of age; some groups suggest that screening be delayed until 25 years of age.

Routine screening for HPV-associated cancers by means of cytologic or HPV testing is currently recommended only for cervical cancer because of the frequencies of cervical precancer and cancer and because of the availability of treatment for cervical precancer. A recent trial of treatment for anal high-grade squamous intraepithelial lesions may lead to changes in screening for anal cancer in some populations.[12]

VACCINES AND VACCINE EFFICACY

The HPV vaccines are based on viruslike particles, which self-assemble spontaneously from pentamers of the L1 major capsid protein of HPV. The first two vaccines that were licensed were a quadrivalent vaccine (Gardasil [Merck], licensed in 2006), which is composed of HPV16, HPV18, HPV6, and HPV11 viruslike particles, and a bivalent vaccine (Cervarix [GlaxoSmith-Kline Biologicals], licensed in 2009), which is composed of HPV16 and HPV18 viruslike particles. The manufacturer of the quadrivalent vaccine later developed a 9-valent vaccine (Gardasil 9, licensed in 2014), which contains viruslike particles of five additional oncogenic types: HPV31, HPV33, HPV45, HPV52, and HPV58. The HPV types that are prevented by 9-valent vaccination account for approximately 90% of HPV-attributable cancers worldwide.[2] Other HPV vaccines have been developed but are not licensed in the United States.[13]

International, randomized, controlled trials involving female adolescents and women 15 to 26 years of age have shown vaccine efficacy of at least 96% for the prevention of cervical precancers (cervical intraepithelial neoplasia grade ≥2 or adenocarcinoma in situ) owing to vaccine-targeted HPV types in per-protocol populations — women who had no evidence of infection with or exposure to a given HPV type at the time of vaccination and had received all three vaccine doses.[14–16] Trials of the quadrivalent vaccine showed 100% efficacy for the prevention of anogenital warts.[14] HPV type–specific antibody developed in almost all the vaccine recipients, and titers were substantially higher than after natural infection. Immunogenicity studies involving children and adolescents 9 to 15 years of age showed antibody titers after vaccination that were noninferior to and higher than those in women in the efficacy trials; these findings led to the licensure of HPV vaccines for use in the younger age group.[17]

Trials of the efficacy of HPV vaccine have also been conducted in men, including a randomized, controlled trial of a quadrivalent HPV vaccine for the prevention of external genital lesions, a substudy evaluating the prevention of anal precancers, and several trials to assess the immunogenicity induced by quadrivalent and 9-valent HPV vaccines.[18–20] In the trial of the quadrivalent HPV vaccine in men, vaccine efficacy for the prevention of vaccine type–related lesions was 90.4% in the per-protocol population.[18]

A randomized trial comparing the 9-valent vaccine with the quadrivalent vaccine in female adolescents and women 16 to 26 years of age showed that 9-valent HPV vaccination resulted in noninferior levels of antibody against HPV6, HPV11, HPV16, and HPV18 and in 96.7% efficacy against the five additional types in the 9-valent vaccine.[21] Approval of the 9-valent vaccine by the Food and Drug Administration (FDA) in 2018 for persons up through 45 years of age was based on a trial of the efficacy of quadrivalent vaccine in women 24 to 45 years of age that showed efficacies of 84.7% in the per-protocol population and 41.6% in the intention-to-treat population for the prevention of a combined end point of persistent infection, cervical intraepithelial neoplasia, or external genital lesions, as well as on immunogenicity data from several trials.[22,23] The lower efficacy in the intention-to-treat population, a result that has been observed in all HPV vaccine trials involving persons with sexual experience, was attributed to previous exposure to one or more HPV vaccine types. There is no evidence from clinical trials that vaccination can prevent the progression of

preexisting infection to disease or can promote the clearance of infection or disease already present at the time of vaccination.[14]

Studies have shown long-lasting protection after vaccination. No waning of protection was detected in the quadrivalent HPV vaccine trial that followed women through 5 years.[24] Among 2121 women in Nordic countries who had been vaccinated in prelicensure trials, there were no cases of HPV16- or HPV18-attributable cervical precancers through at least 12 years of follow-up.[25] Long-term protection in women has also been reported after 9-valent vaccination.[26] In men, quadrivalent HPV vaccination provided long-term protection in a trial that had up to 10 years of follow-up.[27] Vaccination produces higher antibody titers than natural infection. Antibody titers decrease initially after vaccination but plateau after approximately 2 years.[14] No minimum protective antibody titer has been identified.

HPV vaccines were initially licensed as a three-dose series; however, the long-lasting high efficacy of HPV vaccine stimulated interest in the use of fewer doses.[28] Subsequent data supported the use of a two-dose series in children and adolescents 9 to 14 years of age. For example, in a trial of a 9-valent HPV vaccine, the geometric mean antibody titers after the receipt of two doses (separated by 6 or 12 months) in girls and boys 9 to 14 years of age were noninferior to and significantly higher than those that occurred after the receipt of three doses (with the second and third doses given 2 months and 6 months, respectively, after the first dose) in female adolescents and women 16 to 26 years of age; more than 98% of the two-dose recipients had seroconversion to all nine HPV types.[29]

Data on single-dose vaccination first came from post hoc analyses of three-dose vaccine trials in which not all women completed the vaccination series. Women who received one dose had lower antibody titers than those who received more doses, but antibodies and protection against vaccine-targeted HPV types persisted through 10 or more years of follow-up.[30–32] Two recent randomized, controlled trials included a single-dose group.[33,34] One trial showed seroconversion rates after one dose of bivalent or 9-valent vaccine that were noninferior to those observed after two or three doses.[34] In the other trial, the efficacy of both the one-dose 9-valent vaccine and the one-dose bivalent vaccine was 97.5% for the prevention of persistent HPV16 and HPV18 infection through 18 months of follow-up.[33]

VACCINE SAFETY

Safety data regarding HPV vaccines from prelicensure vaccine trials and from more than 15 years of postlicensure monitoring provide extensive reassuring evidence regarding safety. Through 2021, more than 135 million doses of HPV vaccine had been distributed in the United States. Early safety monitoring data showed that syncopal episodes can occur after HPV vaccination, as can occur after other vaccinations in adolescents; recommendations were made for adolescents to be seated when vaccinated and to be observed after the immunization. U.S. vaccine safety monitoring systems as well as special evaluations[35] and postlicensure studies in other countries have not confirmed any other safety signals aside from rare allergic reactions. Large population-based evaluations of general safety, death, autoimmune conditions, and neurologic conditions have shown no safety concerns.[36,37]

HPV VACCINATION PROGRAM IN THE UNITED STATES

Since 2006, routine HPV vaccination has been recommended for girls 11 or 12 years of age; vaccination can be started at 9 years of age. Boys were included in the vaccination program in 2011. Vaccination is also recommended through 26 years of age for previously unvaccinated persons (catch-up vaccination). Ideally, vaccination should occur before the onset of sexual activity. In 2019, shared clinical decision making was recommended for persons 27 to 45 years of age, after the FDA expanded the age indication for the 9-valent vaccine (Table 2). Although three HPV vaccines are licensed in the United States, almost all the vaccine used through 2015 was quadrivalent HPV vaccine.[38] Since the end of 2016, only the 9-valent HPV vaccine has been marketed in the United States.

HPV vaccination coverage has increased gradually but remains lower than the approximately 90% coverage that has been achieved for other vaccines recommended for adolescents.[39] Coverage is monitored among adolescents 13 to 17 years of age by the National Immunization Survey–Teen.[39] By 2021, a total of 79% of girls and 75% of boys had received at least one dose of HPV vaccine; the percentages with up-to-date vaccination were 64% and 60%, respectively (Fig. 2). Because recommendation from a health care provider is the strongest predictor of vaccination, efforts to increase coverage have focused on providing education, tools, and communication messages for health care providers. Best practices include focusing on HPV vaccination as cancer prevention; sending reminders by mail, telephone, or text message; and discussing and recommending all approved vaccinations for adolescents at the same visit.[40,41] Evidence suggests that HPV vaccinations, as well as other routinely recommended vaccinations, have decreased during the coronavirus disease 2019 pandemic.[42] Coordinated efforts between health care providers and public health officials are needed to provide catch-up vaccinations to persons who missed vaccinations earlier and to address vaccine hesitancy.

EFFECTS OF VACCINATION ON INFECTION AND DISEASE

After the introduction of HPV vaccination programs, decreases in the incidence of HPV-attributable cancers take years or decades to realize. However, dramatic decreases in other outcomes have been observed soon after vaccine introduction. Within the first 4 years of the U.S. vaccination program, despite modest coverage among adolescent girls, the prevalence of HPV vaccine–type genital infection among girls and women 14 to 19 years of age decreased by 56%.[43] Twelve years after the program was introduced, the prevalence of HPV vaccine–type infection had decreased by 88% among adolescents 14 to 19 years of age and by 81% among persons 20 to 24 years of age (Fig. 3).[45] Decreases in the prevalence of HPV vaccine–type infection that have been observed among unvaccinated persons indicate herd effects from the vaccination program. The prevalences of anogenital warts and the incidence of recurrent respiratory papillomatosis have also decreased.[46,47]

Cervical precancers are difficult to monitor because detection relies on screening, and screening recommendations have changed in recent years. Nonetheless, between the 2008–2009 period and the 2015–2016 period, there was a 77% reduction in the detection of HPV16- and HPV18-attributable cervical precancers among women 20 to 24 years of age who had undergone screening.[48] Other countries with HPV vaccination programs

have also observed decreases in the prevalences of HPV infection, anogenital warts, and cervical precancers.[49] Postlicensure monitoring has shown effectiveness against precancer end points, similar to end points used in vaccine trials. More recently, population-based studies in several European countries have shown a high effectiveness of HPV vaccine against cervical cancer.[50–52]

AREAS OF UNCERTAINTY

The immunogenicity induced by HPV vaccination has been studied in immunocompromised persons; however, data on efficacy are limited.[53] Some studies have shown lower titers after vaccination in persons with human immunodeficiency virus (HIV) infection than in those without HIV infection. A study involving men 16 to 26 years of age who have sex with men and were living with HIV infection showed high vaccine efficacy against anal squamous intraepithelial lesions among participants who did not have evidence of previous exposure to HPV vaccine types.[54] Questions remain regarding the duration of vaccine-induced immunity in persons vaccinated during adolescence who later become infected with HIV.

Questions about potential increases in the prevalence of disease due to HPV types that are not targeted by vaccination (so-called type replacement) have been raised. However, the investigations that have been conducted to date have not shown any consistent concerns.[55,56]

The evidence supporting single-dose HPV vaccination[30–34] led to the modification of the 2022 World Health Organization recommendations to include an option for single-dose vaccination in some age groups.[13] Further studies are ongoing, including a randomized trial comparing one dose with two doses[57]; additional data are expected over the next few years. An increasing number of countries are recommending vaccination with a single dose.

Some studies have suggested a lower risk of recurrent cervical dysplasia among persons who receive HPV vaccination around the time of surgical treatment. High-quality randomized trials are needed to inform clinical guidance.[58]

Oropharyngeal cancer is now the most common HPV-attributable cancer in the United States; most cases are caused by HPV16.[6,7] Although there are no data from clinical trials showing that HPV vaccines prevent these cancers, in 2020, the 9-valent HPV vaccine received an FDA indication for the prevention of HPV-attributable oropharyngeal and other head and neck cancers, with the stipulation that a well-controlled trial be conducted to evaluate the prevention of persistent oral infection with vaccine-targeted HPV types. This trial is ongoing.[59]

GUIDELINES

The CDC Advisory Committee on Immunization Practices (ACIP) currently recommends routine vaccination for all children at 11 or 12 years of age; vaccination can be started at 9 years of age (Table 2).[22] The ACIP also recommends vaccination through 26 years of age for previously unvaccinated persons (catch-up vaccination) and shared clinical decision making regarding vaccination for persons 27 to 45 years of age. Table 2 shows the currently recommended number of doses according to age at the initiation of vaccination. Vaccination

is recommended regardless of known HPV infection, HPV-associated precancer lesions or abnormal cervical cytologic findings, or anogenital warts. The recommendations in this article are consistent with the ACIP recommendations.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette presents clinical questions about HPV vaccination in the age range for catch-up vaccination. Ideally, HPV vaccination should be given in children 9 to 12 years of age; however, given that this patient is 24 years of age, she is within the age group for which catch-up vaccination is recommended. Because she is starting vaccination after her 15th birthday, three doses are currently recommended. Persons who are vaccinated after becoming sexually active might have already been exposed to one or more HPV types. Although HPV vaccination will not prevent or affect the progression or clearance of any existing infection, it will protect from infection with other HPV types targeted by the 9-valent vaccine. Screening for cervical cancer is not needed before vaccination. However, the patient should undergo screening for cervical cancer and sexually transmitted infections according to established guidelines for her age group.[10,11] Cervical cancer screening at regular intervals is recommended regardless of a patient's HPV vaccination history.

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Key Clinical Points

HUMAN PAPILLOMAVIRUS VACCINATION

- Human papillomavirus (HPV) is a common sexually transmitted virus. Most HPV infections clear or become undetectable within 1 to 2 years, but persistent infection can lead to cervical, vaginal, vulvar, penile, anal, or oropharyngeal cancer.
- Among the oncogenic HPV types, HPV16 is the most likely type to progress to cancer and causes most of the HPV-attributable cancers in women and men.
- HPV vaccines target HPV types that cause most HPV-attributable cancers. In clinical trials, vaccines had high efficacy for the prevention of HPV vaccine–type attributable precancers. Protection after vaccination is long-lasting.
- In the United States, routine HPV vaccination is recommended at 11 or 12 years of age; vaccination can be started at 9 years of age. Vaccination is recommended through 26 years of age for previously unvaccinated persons. Shared clinical decision making regarding vaccination is recommended for some persons 27 to 45 years of age.
- Screening for cervical cancer, according to established guidelines, is recommended regardless of HPV vaccination history.

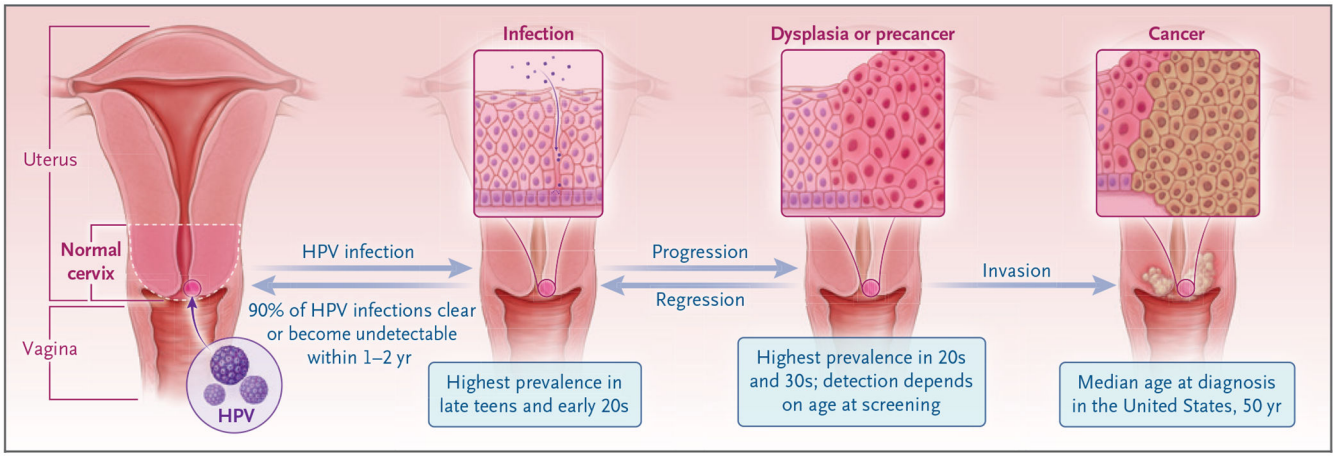

Figure 1. Natural History of Human Papillomavirus (HPV) Infection and Progression to Cervical Cancer.

Shown are the uterine cervix and histologic changes in the cervix from infection, precancer, and cancer. HPV infection occurs most often through sexual contact, and peak prevalence is around the age of first sexual encounters. HPV infects the basal epithelial cells, most often at the endocervical–ectocervical junction, where epithelial disruption allows access. Most HPV infections clear or become undetectable within 1 to 2 years, but a small percentage persist and progress to precancers over periods of months to years. Most precancers regress, but a small percentage of persistent lesions progress to invasive cancer, most commonly over a period of more than a decade. The delay between precancer and cancer allows screening to be effective in detection of early lesions. The treatment of precancers detected by means of screening can prevent invasive cancer. HPV vaccination prevents infection and therefore also precancers and cancers.

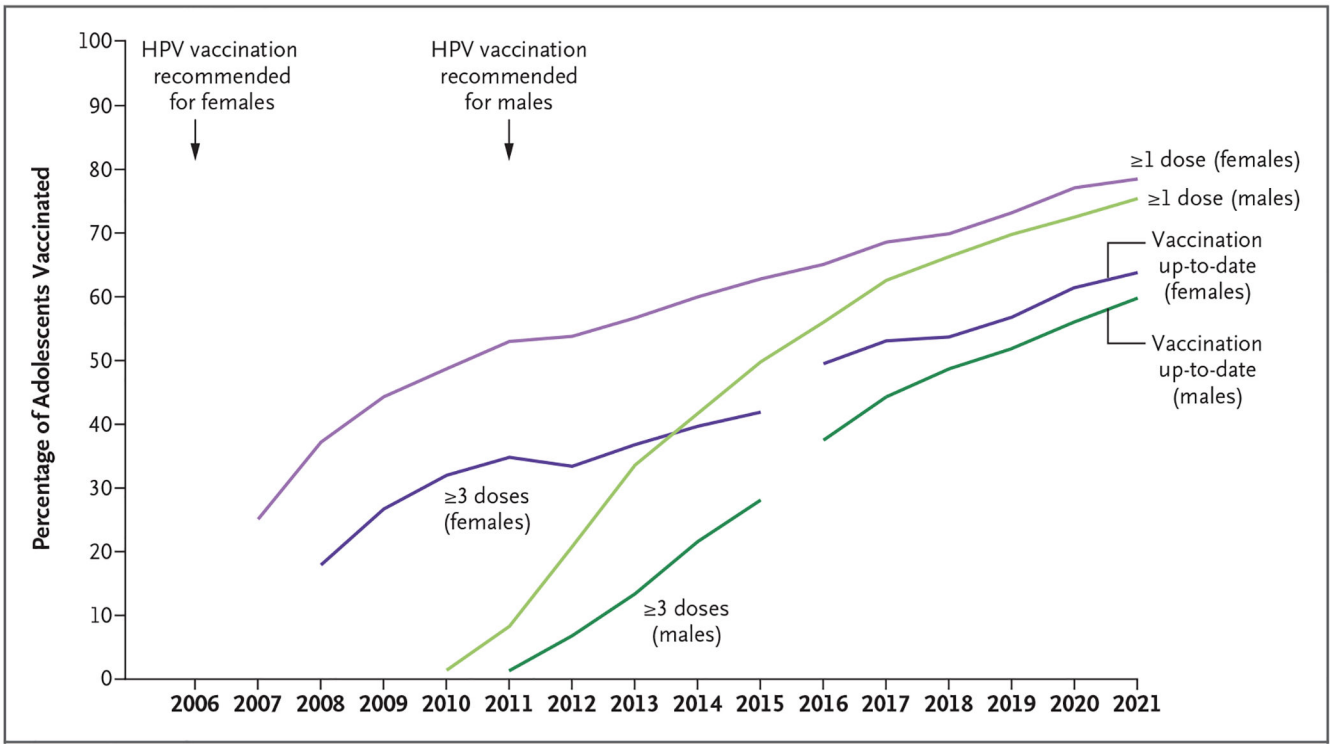

Figure 2. Estimated Coverage of HPV Vaccine among Adolescents 13 to 17 Years of Age, According to Sex and Survey Year, from the National Immunization Survey–Teen, 2007–2021.

Data are from the National Immunization Survey–Teen.[39] The Advisory Committee on Immunization Practices (ACIP) revised the recommended HPV vaccination schedule in late 2016.[38] The schedule changed from a three-dose series to a two-dose series, with appropriate spacing between receipt of the first and second doses, for immunocompetent adolescents initiating the series before their 15th birthday. Three doses are still recommended for adolescents initiating the series at 15 years of age or older. Because of the change in the schedule, the figure includes estimates for the receipt of at least three doses of HPV vaccine during the 2006–2015 period and for up-to-date status of HPV vaccination for the 2016–2021 period. The ACIP recommendation for routine HPV vaccination was made for female adolescents in 2006 and for male adolescents in 2011; up-to-date status for HPV vaccination was defined as the receipt of at least three doses and also as the receipt of two doses when the first HPV vaccine dose was administered before 15 years of age with an interval of at least 5 months between the first and second doses.

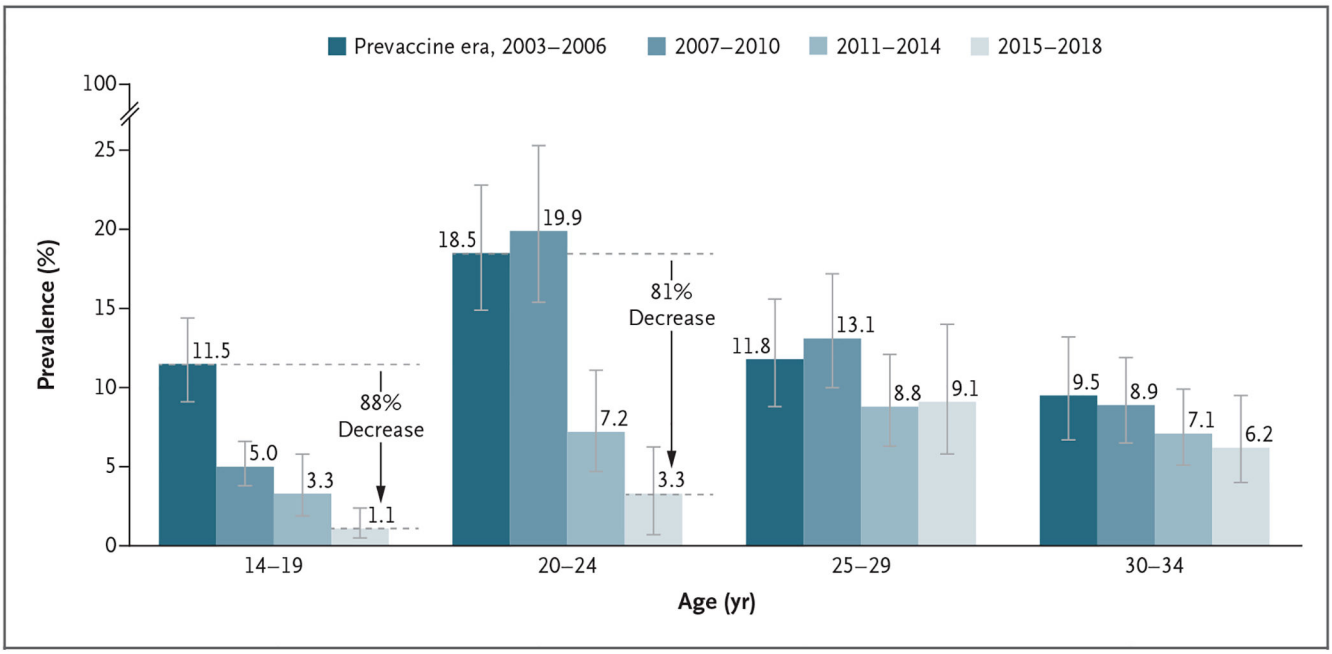

Figure 3. Prevalence of Quadrivalent Vaccine–Type Infection among Girls and Women, According to Age Group and Survey Period, from the National Health and Nutrition Examination Surveys, 2003–2018.

Adapted from Markowitz et al.,[43] Oliver et al.,[44] and Rosenblum et al.[45] Quadrivalent vaccine–type HPV infection includes types HPV6, HPV11, HPV16, and HPV18. The decreases in the prevalence that are shown for persons 14 to 19 years of age and 20 to 24 years of age are for the 2015–2018 survey period as compared with the prevaccine era and are based on adjusted prevalence ratios. I bars indicate 95% confidence intervals.

Table 1.

Cancers Associated with and Attributed to Human Papillomavirus (HPV) Infection in the United States, 2015–2019.[*]

Cancer Site	No. of HPV-Associated Cancers	Percentage of Cancers Probably Caused by Any HPV Type	Estimated No. of Cancers Probably Caused by Any HPV Type[†]		
			Among Females	Among Males	Among Both Sexes
Cervix	12,293	91	11,100	0	11,100
Vagina	879	75	700	0	700
Vulva	4,282	69	2,900	0	2,900
Penis	1,375	63	0	900	900
Anus[‡]	7,531	91	4,700	2,200	6,900
Oropharynx	20,839	70	2,300	12,500	14,800
Total	47,199	79	21,700	15,600	37,300

[*]Adapted from data provided by the Centers for Disease Control and Prevention (CDC) (https://www.cdc.gov/cancer/hpv/statistics/cases.htm). Data were compiled from population-based cancer registries that participate in the CDC National Program of Cancer Registries and in the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. The data met the criteria for high-quality data for all years in the 2015–2019 period, with coverage of 98% of the U.S. population.

[†]Estimates were based on studies that typed HPV. Most were high-risk HPV types that are known to cause cancer.[7] Estimates were rounded to the nearest 100. Estimated counts may not sum to the expected total because of rounding.

[‡]Anal cancer includes anal and rectal squamous-cell carcinoma.

Table 2.

Recommendations for HPV Vaccination in the United States.*

Variable	Recommendation
Age group	
11 or 12 yr; can be initiated starting at 9 yr	Routine-vaccination age group
13–26 yr	Catch-up vaccination for previously unvaccinated persons
27–45 yr	Shared clinical decision making for previously unvaccinated persons
No. of doses	
Among persons 9–14 yr of age at vaccine initiation	2 doses, with the second dose administered 6–12 mo after the first dose†
Among persons ≥15 yr of age at vaccine initiation or those with an immunocompromising condition	3 doses, with the second dose administered 1–2 mo after the first dose and with the third dose administered 6 mo after the first dose‡

*These recommendations are those of the CDC Advisory Committee on Immunization Practices.[22]

†In the two-dose schedule, the minimum interval between the first and second doses is 5 months.

‡In the three-dose schedule, the minimum intervals are 4 weeks between the first and second doses, 12 weeks between the second and third doses, and 5 months between the first and third doses.