

REVIEWS

A Review of the Impact and Discussion of the Future Outlook Regarding the HPV Vaccination Valencies

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The Human papillomavirus (HPV) vaccine was the first vaccine developed to protect against a sexually transmitted disease. Throughout the past decade, bivalent (2vHPV), quadrivalent (4vHPV), and nonvalent (9vHPV) vaccines have been widely distributed throughout the world. In this narrative review, we will discuss the pathologic and immunologic efficacy of the different HPV vaccine valencies, specifically focusing on their ability to prevent genital warts and malignant neoplasms. Although vaccine efficacy and safety remain high across all valencies, there is growing vaccine hesitancy towards the HPV vaccines which is detrimental towards the establishment of herd immunity. We will examine the challenges associated with tracking and administering a multi-dose regimen in both developing and developed nations and discuss new findings that suggest vaccination with a single dose against HPV confers significant immunity towards the virus. We conclude that a one dose HPV vaccine solution would be a worthwhile investment, and instrumental in achieving herd immunity against HPV in both developed and developing nations.

Introduction

The human papillomaviruses (HPVs) are DNA viruses that can cause proliferative epithelial lesions that are strongly associated with the development of malignant tumors. It is also the most common infection of the female reproductive tract, and one of the most common sexually transmitted infections around the world.¹ In the United States, there are around 42 million people infected with HPV, and around 13 million develop new infections every year.^{1,2} HPV is capable of infecting basal epithelial cells to cause a wide variety of pathologies. These range from benign lesions, such as warts on the skin of the feet and hands, to neoplastic growths on the genitals, oropharynx, cervix, vulva, vagina, or penis.¹

There are roughly 30 different types of HPVs that have been identified as sexually transmittable, and in 99.7% of cervical squamous cell carcinoma cases, at least 1 of these HPV strains has been found in the malignancy. However, not all HPV infections lead to cervical cancer. In fact, most of these infections only induce transient changes in the cervical epithelium, with 90% of these lesions resolving spontaneously within 1 to 3 years.¹

In 2015, cervical cancer was diagnosed in 526 000 women globally and caused 239 000 deaths.² Most of these diagnoses occurred in women who were in their third and fourth decade of life. Because the mortality rate for cervical cancer is so high, screening and early detection programs are important in reducing morbidity and mortality. In addition to vaccination, HPV testing and cervical cancer screening are necessary to increase the rate at which the virus and malignancies are detected early, as this may reduce the harms caused secondary to infection.

Given the prevalence of HPV and strong connection to cervical cancer, research dedicated to vaccine development commenced in the 1980s. The vaccine is noteworthy, being the first vaccine to protect against a sexually transmitted infection. Its design centers on viruslike particles that mimic the L1 major capsid protein. The body responds by producing antibodies that bind to these particles, thus preventing future infection. Immunization poses no risk of infection because of its basis of a single viral subunit. The first 2 licensed prophylactic vaccines were bivalent and quadrivalent. A third type, the 9-valent vaccine, arrived shortly after.³ Now, the public health recommendation in the United States is for children aged 11 to 12 years to receive a 2-dose series of the 9-valent vaccine.⁴

Since its integration into the standard immunization schedule in 2006, HPV infections have decreased by 88% among teenage girls and 81% among young adult women in the United States.⁴ Globally, the vaccine has become part of more than 100 national public health programs. These programs include both adolescent girls and boys. Hesitancy towards immunization mainly stems from fear of adverse effects or the cultural taboo surrounding sexually transmitted infections.³ Despite these roadblocks, by virtue of the vaccine, HPV-related diseases are rapidly decreasing and will continue to do so as immunization programs expand.

HPV Vaccines and Protection From Malignancies

Since the emergence of the HPV vaccine, studies have been conducted to demonstrate its efficacy in minimizing the cosmetic issues and discomfort associated with cutaneous warts, which is theorized to be due to the cross protection that enables the immune system to rapidly undergo a systemic response. As research continues, the noteworthy question to ask has not been whether or not the vaccine is efficacious, but rather how can the vaccine be made better? The research, therefore, tailors towards valencies and discrepancies between them. The current recommended vaccination regimens for HPV in the United States are 2 or 3 doses of the Gardasil 9 (Merck) 9-valent HPV vaccine, with the 2-dose vaccine consisting of 2 doses given 6 to 12 months apart, and the 3-dose vaccine given as 2 doses a month apart, with the third dose after 6 months.⁵ In addition to preventing HPV infection, a study by Shin JJ et al⁶ in 2020 showed that the HPV vaccine treated

Table 1. Types of HPV Vaccines^a

Vaccine	Valency	HPV strain coverage
Cervarix	2	16 and 18
Gardasil	4	6, 11, 16, and 18
Gardasil-9	9	6, 11, 16, 18, 31, 33, 45, 52, and 58

^aThese human papillomavirus (HPV) vaccines were approved by the US Food and Drug Administration and their valencies. Gardasil 9 is the vaccine currently being distributed in the United States.

recalcitrant genital warts in 5 patients. In this study, with only a 3-dose regimen of the nonavalent HPV vaccine over 6 months, 62.2% of those who had warts were able to see full clearance of all warts, while 28.9% saw a decreased number of warts.⁶ The wart clearance response rates have been reported in other quadrivalent studies, but at a much lower range—from 43% to 46%—indicating that the type of vaccine used is a determinant in wart regression. In other words, valency could be a key condition that determines efficacy. However, while the nonavalent option seems promising, this series of vaccination is novel to the HPV vaccine research field, and has not been extensively studied in wart prevention. Many trials have been single-grouped and noncontrolled, requiring more rigorous analysis before adopting the nonavalent vaccination specifically for treatment of warts. It is abundantly clear, however, that the HPV vaccine has impacted the lives of those who are afflicted with oral, anal, or genital warts, and that the direction is gearing towards the 9-valent HPV (9vHPV) vaccine.

While there are well-grounded reasons to receive the HPV vaccination for warts, arguably the most important benefit is its prophylactic effect towards potential malignant neoplasms, some of which are well-studied, eg, cervical and vaginal cancers, but some of which the research is just now focusing on, eg, anorectal cancers. Thus, when comparing the vulvar and cervical cancer rates before the HPV vaccine was available in 2006 and afterwards, individuals who received the vaccines demonstrated a decreased risk for vulvar squamous cell carcinoma (0.18) and cervical carcinoma (0.41) in patients 15 to 24 years old.⁷ Similar results were seen for those 25 to 34 years old, albeit less dramatically: 0.54 for vulvar squamous cell carcinoma and 0.91 for cervical carcinoma. Curiously, the rate ratio of anorectal cancers actually increased after 2006 (1.10) which could be explained by the low incidence rate (per 1 million people, 1.64 before 2006 and 1.8 after 2006), advancements in screening techniques throughout the decade, and the inability to treat anal cancers as aggressively as other genital cancers due to increased risk of health complications.⁸ There are a few types of cancers that have a rate ratio near 1.0, eg, oropharyngeal squamous cell carcinoma, which shows that vaccination has not been shown to be very efficacious. These numbers can be expounded by lack of vaccination in men, which is especially plausible when comparing how the rates of female-specific carcinomas decreased (eg, cervical) while all-inclusive cancers (eg, oropharyngeal) have

maintained prominence. Another explanation may be ineffective marketing or even insufficient time to display the full effects of the HPV vaccine on carcinomas, due to natural development of carcinomas as age increases. The HPV vaccine research field is lacking in this particularly important field, especially for men's health and HIV/AIDS-afflicted individuals.

The quadrivalent vaccine has already been implemented in many other areas of the world as part of a mandatory series of public health requirements, such as Australia via the National HPV Vaccination Programme. Many of the effects seen in the prior 2 discussions on warts and neoplasm rates were seen by Patel et al,⁹ (ie, diminishing rates of both); however, the focus in HPV vaccination is currently on the effects of herd immunity that are observed because the warding off of virus on those who are unvaccinated via those who are vaccinated can only be seen after many years of vaccination protocols to boost population immunity. Among men who were not vaccinated, genital wart hospitalizations decreased from 38.3% in 2006-2007 to 21.2% in 2010-2011. Furthermore, diagnoses of genital warts decreased from 11.3% in 2004-2005 to 2.8% in 2013-2014, a near 9% drop. Another study found that as vaccination rates in a group of women aged 13 to 26 years increased from 0% to 84.3%, the detection rate of HPV went from 35% to 6.7% in vaccinated and 32.4% to 19.4% in unvaccinated women.¹⁰ The current research highlights the marked improvement that the developed HPV vaccine holds for herd immunity: there is a marked decline in the rates of genital warts that, although more research needs to be performed, might mirror cancer rates in the future through this aspect of immunity. This unique communal and societal benefit is another addition to the many impacts that HPV vaccination has brought since its conception, especially critical to those who cannot receive it such as those with immune-compromising ailments.

HPV Vaccine Adverse Effects and Challenges

Although the quadrivalent HPV (4vHPV) and 9vHPV vaccines are effective against genital warts and malignant neoplasms, there have been some minor adverse effects reported as well as contraindications and issues with vaccine production and distribution.

Gardasil, which is the predominant quadrivalent and nonavalent vaccine used in the United States, is widely considered a highly safe vaccine.¹¹ The AICP currently advises the administration of the vaccine to everyone who has not been vaccinated and is between the ages of 9 and 26.¹² The only statistically significant adverse events found in a study with more than half a million vaccines given in the United States were nonspecific adverse events occurring the first few days after vaccination.¹³ The most common adverse events were injection-site reactions and headache, but the attributable risks for these were as low as 0.001% of all doses.¹³ Other rare adverse effects occurring after receiving the HPV vaccine include general fatigue, widespread pain, motor dysfunction, sleep disturbance, learning impairment, and menstrual

abnormalities.¹⁴ However, it is important to note that these adverse effects are correlative and causation between the vaccine and these symptoms was not established.¹⁴ One cross-sectional analysis using vaccine adverse effects found that there were approximately 29.4 total adverse events per 100 000 doses reported in 2018 and 1.5 per 100 000 were deemed serious adverse events.¹¹ A separate 2016 study of more than 15 000 patients receiving the vaccine found that there was no difference in adverse events between the quadrivalent and nonvalent vaccines.¹⁵ Furthermore, there was no difference in adverse events across all age groups.¹⁵

There are few contraindications to the HPV vaccine, but there are some individuals who should not receive the vaccine. Those allergic to components of the HPV vaccine should not be vaccinated due to rare vaccine-related anaphylactic events. 9vHPV is a recombinant vaccine expressed in yeast, so those with previous hypersensitivity reactions to yeast are contraindicated. The bivalent vaccine is contraindicated in individuals with latex allergies, and anyone with a previous hypersensitivity reaction to any HPV vaccine should not receive the vaccine again. All HPV vaccines are currently not recommended for pregnant women. Not enough research has been done on the HPV vaccine in pregnant women, although animal trials have shown no adverse developmental effects in pregnant rats. The Centers for Disease Control and Prevention does not recommend pregnancy testing before administering the vaccine, but if one becomes pregnant after receiving a dose of the vaccine, the remaining doses are delayed until after pregnancy.¹⁶

Distribution of the 9vHPV vaccine in the United States has been widely successful but increasing vaccine hesitancy and service delivery issues are a significant reason why only 58% of adolescents are up to date on their HPV vaccination. A mixed-method study in primary care centers in New Mexico found strong approval of the 9vHPV vaccine among both physicians and patients. However, lagging delivery systems that do not track vaccination status across health care systems and an inability to set reminders about vaccine dosage lead to eligible patients not receiving the vaccine. Although improvements in vaccine stability may help distribution in developing nations, in the United States, patient education on the HPV vaccine and improved or centralized health care databases will ultimately lead to the greatest improvement in vaccination status. Increasing the percentage of the population vaccinated against HPV will help protect vaccinated individuals and will also contribute to community immunity against HPV-associated diseases.¹⁷

Comparing Immunogenicity of HPV Vaccines

Vaccine development is a complicated process that requires exhaustive measures to create a balance between coverage and efficacy against the disease. Greater coverage of different strains of HPV in a single vaccine is desirable,

but it may inadvertently lead to weaker immunogenicity. For HPV, the majority of cases are attributed to valencies 16 and 18.⁴ Genital warts are most commonly caused by HPV6 and 11.¹⁸ All HPV vaccines include these strains, but are of varying valencies. Three such vaccines have been approved by the US Food and Drug Administration for distribution: bivalent Cervarix (HPV 16 and 18), quadrivalent Gardasil (HPV 6, 11, 16, and 18), and 9-valent Gardasil 9 (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58). The lattermost 9-valent has been the only HPV vaccine distributed in the United States since 2017 because of its wider range of protection. Worldwide, all 3 types continue to be used.⁴ Examining the effects of these vaccines is important, as type replacement is not predicted to occur with a stable virus like HPV. Without an evolving virus, the common valencies are predicted to remain HPV 16 and HPV 18.¹⁹

In general, all types of the HPV vaccine are effective and boast strong immunogenicity.¹⁹ They share a mechanism of action that induces neutralizing antibodies against HPV infection. Therefore, postvaccination geometric mean titers (GMTs) of neutralizing antibodies are one way to compare vaccine efficacies. This parameter measures antibody response after vaccination.²⁰ Moreover, seroconversion approached 100% for all types of the vaccine after a 3-dose series. Antibody levels remained stable for more than 10 years after vaccination. Reported vaccine efficacy was greater than 90% for women aged 15 to 26 years.¹⁹

The immunological response to each of these vaccines is effective, but not equal. In a clinical trial study, Finnish women aged 16 to 17 years were administered either a bivalent (HPV 16 and 18) or quadrivalent (HPV 6, 11, 16, and 18) 3-dose vaccine series. For both HPV 16 and 18, the GMT was reported to be higher in the bivalent vaccine for all timeframes (ranging for 2-12 years). Notably, 11 to 12 years after vaccination, the GMT ratio of bivalent vs quadrivalent vaccines was 6.08 for HPV 16 (18 366 vs 3021). For HPV 19, the GMT ratio was 13.1 (4708 vs 358). Fifteen percent of those who received the quadrivalent vaccine did not have detectable HPV 18 antibodies 2 to 4 years after vaccination. These data indicate that the bivalent vaccine is better suited for long-term protection against the 2 most common strains of HPV.²⁰

As expected, quadrivalent recipients had higher prevalence of the HPV 6 antibody. The reported GMT ratio of bivalent vs quadrivalent vaccines was 0.04 for 11 to 12 years after vaccination. No data on HPV 6 response were included. Cross-protection against HPV valencies not included in the vaccine was also examined. Antibodies against HPV 31, 33, 45, 52, and 58 were more prevalent in those who received the bivalent vaccine. Specifically, the differences in prevalence ranged from 15% to 36% 5 to 12 years after vaccination. Among those who did have cross-protection, comparable long-term protection was displayed.²⁰

Table 2. Geometric Mean Titer (GMT) Values for Human Papillomavirus (HPV) Vaccines

HPV strain	GMT, mMU/mL		
	2vHPV	4vHPV	9vHPV
6	136	3099	135.4
11	NR	NR	87.8
16	20113	3429	490.4
18	4508	392	150.0
31	179	120	125.8
33	107	186	65.3
45	79	89	48.9
52	120	119	69.7
58	118	204	85.6

Bivalent (2vHPV) and quadrivalent (4vHPV) HPV vaccine data are from females aged 16 to 17 years from Finland. Data points are measured 8 to 10 years after vaccination and adapted from the 2021 Mariz et al study.²⁰ Nonavalent HPV (9vHPV) vaccine data are from females aged 16 to 26 years from various countries. Data points are measured 7.5 years after vaccination and adapted from the Olsson et al study.¹⁸ GMTs of neutralizing antibodies measure antibody response after vaccination. All types of vaccines are effective against HPV. NR indicates not reported.

The 9-valent vaccine was studied in a long-term follow-up study consisting of women from 13 countries aged 16 to 26 years. They were given a 3-dose series of the 9-valent vaccine. At 7.5 years, the GMT values for HPV 16 and 18 were 438.2 and 83.8, respectively. Seropositivity values at 7.5 years ranged from 100% (HPV 16 and 31) to 97.2% (HPV 18). No high-grade intraepithelial neoplasia was seen in any of the recipients either. It is evident from these data that the 9-valent vaccine is successful in maintaining immunity from its targeted valencies.¹⁸

As seen in Table 1, all HPV vaccines are suitable candidates for protection against the virus and its malignant effects. The bivalent vaccine boasts the strongest efficacy for HPV 16 and 18 by more than a factor of 10. The quadrivalent vaccine is best for protection against HPV 6, 33, 89, and 58. However, the 9-valent vaccine is the ideal vaccine because it offers suitable protection against the 9 most prevalent strains of HPV. It should be noted that the population and timeframe for each study are slightly different and, therefore, these comparisons are not concrete.^{18,20}

Vaccine Cost and Use Globally

In many cases, the projected cost of a vaccination regimen can deter institutions from implementing them. Thus, although the 9-valent HPV vaccine is the most efficacious in conferring immunity to a multitude of HPV strains, its cost may be an impediment to low-resource communities. The bivalent and quadrivalent vaccines, however, still offer significant reductions in cervical cancer incidence, albeit to a lesser extent than the 9-valent vaccine.²¹ It is, therefore, important for policymakers to take into consideration the benefits and costs associated with the different HPV vaccines when planning public health interventions.

The World Health Organization currently recommends that girls aged 9 to 14 years receive at minimum 2 doses of the HPV vaccine to protect against cervical neoplasms. These recommendations are based on scientific evidence and aim to reduce the burden of HPV-related diseases worldwide.²² However, obtaining 2 doses is a challenge for many communities around the world, and thus if a 1-dose regimen were shown to be effective, this could possibly increase vaccine uptake and substantially decrease associated costs.

A study by Sankaranarayanan et al²³ enrolled 17729 girls between the ages of 10 and 18 years from 4 different regions in India. These girls then received either 1, 2, or 3 doses of the quadrivalent HPV vaccine at 0, 2, and 6 months. Immunogenicity was measured by the level of antibodies against major capsid protein L1 of HPV 6, 11, 16, and 18 and reported as the mean median fluorescence intensity in the serum of the vaccinated girls. These levels were obtained by measuring antibody titers using the competitive Luminex Immunoassay at baseline and at 7, 18, 24, and 36 months after the first dose of the HPV vaccine. The results showed that 1 dose of the vaccine was less immunogenic than 2 or 3 doses, but still provided significant protection against HPV infection. Vaccine efficacy against HPV 16/18–related cervical intraepithelial neoplasia grade 2 or worse (CIN2+) and CIN3+ was also evaluated based on histological analysis of cervical biopsy samples obtained during follow-up visits. The study showed that 2 doses of the vaccine provided similar levels of protection to 3 doses, which was shown by antibody levels at 36 months, where more than 99% of girls in the 2-dose group and 91% of girls in the 1-dose group had antibody concentrations equal to or higher than the lowest median fluorescence intensity value in the 3-dose group.²³ The study thus suggested that a 2-dose vaccination regimen might be effective in preventing cervical cancer in girls in India since the logistical resources needed to distribute 1 dose would be much less than that needed to distribute 2 doses, but more research needs to be done on the long-term efficacy of a 1-dose vaccine.

A similar study was published in 2022 by Watson-Jones et al²⁴ that came to a similar conclusion: that a 1-dose vaccine may be plausible as an alternative in areas where access to multiple doses may be limited. This study enrolled 930 girls between the ages of 9 and 14 years in Tanzania who were then randomized to receive either 1, 2, or 3 doses of the Cervarix (2vHPV) or Gardasil 9 vaccine. The efficacy of the vaccination was then gauged using measured levels of the HPV 16 and 18 antibodies. This study found that 1 dose of either HPV vaccine was noninferior to the 2- or 3-dose regimen when their HPV 16 IgG seropositivity at 24 months was compared; however, it did find that the HPV 18 IgG seropositivity did not meet the study's noninferiority criteria when compared with the 2- or 3-dose regimens. Nevertheless, more than 98% of the girls in all groups had HPV 18 antibodies.²⁴ The results from this study fall in line with previous studies that suggested 1-dose HPV vaccine regimens to be highly effective in protecting

against HPV infection. This study was not without limitations, however. The study was limited by the short 24-month follow-up period, and the absence of a clinical evaluation of this method of vaccination's efficacy. Thus, more research would need to be conducted on the clinical end to ensure its real-world effectiveness.

Because the burden of cervical cancer and HPV infection is borne mostly by low- and middle-income countries and communities, studies such as these offer a cost-effective proposition to reducing the burden of HPV-related diseases. The high seropositivity rates in both of the studies' populations (adolescent girls in both India and Tanzania) hold much promise, especially because their immune responses were durable and stable for at least 2 years in the Tanzania group and 3 years in the India group. These results are significant for medically underserved communities around the globe, whose members face significant difficulty in receiving reliable preventive care.

Conclusions

Although treatment and vaccination against HPV strains of all kinds has progressed significantly only in the past decade, debates are still ongoing about the best course of action and protocol. In this review, we have discussed the values and limitations of different valency HPV vaccinations in terms of efficacy towards pathology and immunogenicity. Finally, we comment on vaccine hesitancy and how to overcome it.

Certainly, the 4vHPV vaccine has held the title as the longest-standing HPV vaccine on the market for its benefits against HPV. Research has shown that it has significant prophylactic effects against genital warts, halting their appearance after vaccination, and many types of cancers, substantially reducing population rates of cervical, vulvar, and vaginal carcinomas. Additionally, the herd immunity effect provided by the 4vHPV vaccine is just now being fully seen due to increased population vaccination, reducing rates of HPV manifestations in unvaccinated individuals by 10%. However, the antibody titers of certain HPV strains seen in persons post-4vHPV vaccine have been lower than any other valency, with some trials even finding that antibodies are nonexistent after half a decade, which could dampen the protective immune effects. It is, therefore, a matter of whether the lower titer levels affect quality of life and pathology resolution.

The 9vHPV vaccine lives up to the promise and fills some of the shortcomings that other valency vaccinations have. Preliminary studies have already shown increased clearance of warts as a treatment option compared with the 4vHPV vaccine, in addition to its prophylactic effects. While it has not been available long enough to examine its effect on cancer rates and herd immunity, the immunogenicity of the 9vHPV vaccine eclipses 4vHPV's own

and maintains antibody titer levels for an additional half decade against the cancer-inducing HPV 16 and 18, holding promise for the aforementioned immune functions.

Although this review did not look at 2vHPV vaccination effects on pathology, there has been encouraging evidence towards its usage due to its antibody titer production in the body, surpassing that of the 4vHPV vaccine with greater coverage of HPV strains. Especially considering the population frequency of HPV 16 and 18-related cancers, it is prudent that we as a society more carefully scrutinize the 4vHPV vaccine on a national level and reevaluate the 2vHPV vaccination, especially considering cost-effectiveness and distribution.

While many studies have shown that the 9vHPV vaccine has been reliable in preventing pathology and raising immunity, the adverse effects are equivalent to the prior valencies: headache, dermatological reactions, fatigue, insomnia, amenorrhea, among others. However, these effects are minor in nature and rare to begin with, with only a 0.029% chance of occurring. Still, they provide a major reason for vaccine hesitancy, along with abortifacient warnings despite animal trials showing no abnormal developmental outcomes.

Decreased adherence to vaccination may also be caused by inconvenience, inaccessibility, or simply forgetfulness, as many health care professionals recommend a 2- to 3-dose series shot. In order to raise the barrier of access on all 3 fronts, it would be judicious to move to a 1-dose regimen of the HPV vaccine, no matter what valency, especially in countries where medical databases and distribution issues make coordinating multiple regimens difficult. Current research has shown that antibody titers in a 2-dose sequence nearly mimic that of the 3-dose sequence at 99%, and 1-dose is close behind at 91%; these are for both the 4vHPV and 9vHPV vaccine. Thus, reducing the dosing schedule of HPV vaccines would increase vaccination rates while minutely affecting the efficacy.

Through tackling distribution issues, education on HPV vaccinations, improved coordination between databases, and advancements that focus on the development of a 1-dose system, the HPV vaccine would be able to reach a greater population, thereby making halting the spread of HPV a goal that is more within reach than previously thought.

Conflicts of Interest

None reported.

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REFERENCES

1. Okunade KS. Human papillomavirus and cervical cancer. *J Obstet Gynaecol.* 2020;40(5):602-608. doi:[10.1080/01443615.2019.1634030](https://doi.org/10.1080/01443615.2019.1634030). PMID:31500479
2. Altobelli E, Rapacchietta L, Profeta VF, Fagnano R. HPV-vaccination and cancer cervical screening in 53 WHO European countries: an update on prevention programs according to income level. *Cancer Med.* 2019;8(5):2524-2534. doi:[10.1002/cam4.2048](https://doi.org/10.1002/cam4.2048). PMID:30993902
3. Markowitz LE, Schiller JT. Human papillomavirus vaccines. *J Infect Dis.* 2021;224(4):S367-S378.
4. Centers for Disease Control and Prevention. HPV vaccine information. Accessed March 27, 2025. <https://www.cdc.gov/vaccines/vpd/hpv/public/>
5. Centers for Disease Control and Prevention. Administering HPV vaccine. November 16, 2021. Accessed June 3, 2025. <https://www.cdc.gov/vaccines/vpd/hpv/hcp/administration.html>
6. Shin JJ, Ghosh T, Kwon T, et al. Efficacy of nonavalent HPV vaccine for treatment of genital warts: a single-arm study. *Vaccines (Basel).* 2021;9(6):578.
7. Guo F, Adekanmbi V, Hsu CD, Berenson AB. Incidence of human papillomavirus-related cancers among males and females aged 15-34 years in the United States. *JNCI Cancer Spectr.* 2023;7:pkad016.
8. Ouhoumane N, Steben M, Coutlée F, et al. Squamous anal cancer: patient characteristics and HPV type distribution. *Cancer Epidemiol.* 2013;37(6):807-812. doi:[10.1016/j.canep.2013.09.015](https://doi.org/10.1016/j.canep.2013.09.015)
9. Patel C, Brotherton JML, Pillsbury A, et al. The impact of 10 years of human papillomavirus (HPV) vaccination in Australia: what additional disease burden will a nonavalent vaccine prevent? *Eurosurveillance.* 2018;23(41):1700737. doi:[10.2807/1560-7917.ES.2018.23.41.1700737](https://doi.org/10.2807/1560-7917.ES.2018.23.41.1700737). PMID:30326995
10. Spinner C, Ding L, Bernstein DI, Brown DR, et al. Human papillomavirus vaccine effectiveness and herd protection in young women. *Pediatrics.* 2019;143(2):e20181902. doi:[10.1542/peds.2018-1902](https://doi.org/10.1542/peds.2018-1902). PMID:30670582
11. Sonawane K, Lin YY, Damgacioglu H, et al. Trends in human papillomavirus vaccine safety concerns and adverse event reporting in the United States. *JAMA Netw Open.* 2021;4(9):e2124502.
12. Osaghae I, Chido-Amajuoyi OG, Shete S. Healthcare provider recommendations and observed changes in HPV vaccination acceptance during the COVID-19 pandemic. *Vaccines (Basel).* 2022;10(9):1515. doi:[10.3390/vaccines10091515](https://doi.org/10.3390/vaccines10091515). PMID:36146593
13. Yih WK, Kulldorff M, Dashevsky I, Maro JC. A broad safety assessment of the 9-valent human papillomavirus vaccine. *Am J Epidemiol.* 2021;190(7):1253-1259. doi:[10.1093/aje/kwab022](https://doi.org/10.1093/aje/kwab022). PMID:33558897
14. Ozawa K, Hineno A, Kinoshita T, Ishihara S, Ikeda SI. Suspected adverse effects after human papillomavirus vaccination: a temporal relationship between vaccine administration and the appearance of symptoms in Japan. *Drug Saf.* 2017;40(12):1219-1229. doi:[10.1007/s40264-017-0574-6](https://doi.org/10.1007/s40264-017-0574-6)
15. Moreira ED Jr, Block SL, Ferris D, et al. Safety profile of the 9-valent HPV vaccine: a combined analysis of 7 phase III clinical trials. *Pediatrics.* 2016;138(2):e20154387. doi:[10.1542/peds.2015-4387](https://doi.org/10.1542/peds.2015-4387)

16. Petrosky E, Bocchini JA Jr, Hariri S, et al. 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.
17. Sussman AL, Helitzer D, Bennett A, Solares A, Lanoue M, Getrich CM. Catching up with the HPV vaccine: challenges and opportunities in primary care. *Ann Fam Med*. 2015;13(4):354-360. doi:[10.1370/afm.1821](https://doi.org/10.1370/afm.1821). PMID:26195681
18. Olsson SE, Restrepo JA, Reina JC, et al. Long-term immunogenicity, effectiveness, and safety of nine-valent human papillomavirus vaccine in girls and boys 9 to 15 years of age: interim analysis after 8 years of follow-up. *Papillomavirus Res*. 2020;10:100203. doi:[10.1016/j.pvr.2020.100203](https://doi.org/10.1016/j.pvr.2020.100203). PMID:32659510
19. Markowitz LE, Schiller JT. Human papillomavirus vaccines. *J Infect Dis*. 2021;224(12 suppl 2):S367-S378. doi:[10.1093/infdis/jiaa621](https://doi.org/10.1093/infdis/jiaa621)
20. Mariz FC, Gray P, Bender N, et al. Sustainability of neutralising antibodies induced by bivalent or quadrivalent HPV vaccines and correlation with efficacy: a combined follow-up analysis of data from two randomised, double-blind, multicentre, phase 3 trials. *Lancet Infect Dis*. 2021;21(10):1458-1468. doi:[10.1016/S1473-3099\(20\)30873-2](https://doi.org/10.1016/S1473-3099(20)30873-2)
21. Jit M. Informing global cost-effectiveness thresholds using country investment decisions: human papillomavirus vaccine introductions in 2006-2018. *Value Health*. 2021;24(1):61-66. doi:[10.1016/j.jval.2020.07.012](https://doi.org/10.1016/j.jval.2020.07.012)
22. World Health Organization. *Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem*. WHO Press; 2020.
23. Sankaranarayanan R, Prabhu PR, Pawlita M, et al. Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study. *Lancet Oncol*. 2016;17(1):67-77. doi:[10.1016/S1470-2045\(15\)00414-3](https://doi.org/10.1016/S1470-2045(15)00414-3). PMID:26652797
24. Watson-Jones D, Changalucha J, Whitworth H, et al. Immunogenicity and safety of one-dose human papillomavirus vaccine compared with two or three doses in Tanzanian girls (DoRIS): an open-label, randomised, non-inferiority trial. *Lancet Glob Health*. 2022;10(10):e1473-e1484.