Published in final edited form as:

Gynecol Oncol. 2020 February ; 156(2): 498–502. doi:10.1016/j.ygyno.2019.10.018.

Human papillomavirus vaccination: Ongoing challenges and future directions

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Abstract

Studies with prophylactic HPV vaccination have demonstrated impressive efficacy, immunogenicity, and safety results; however, the implementation and uptake in both low and high-income countries continues to be challenging. Since 2006, administration guidelines have undergone multiple updates regarding age, dosing schedule, and gender. Despite these changes, the basic tenet remains the same: prioritize immunization before initiation of sexual activity and subsequent exposure to HPV. The importance of immunizing males and females equally and the role for catch-up vaccination in late adolescent and adulthood has also been supported by subsequent research. Very recently, the FDA approved to expand the range of eligible patients for the non-avalent (9vHPV) vaccine to women and men from age 27 to 45 for the prevention of HPV-related cancers and diseases. Furthermore, members of the ACIP voted to recommend that individuals between ages 27 and 45 who have not yet been vaccinated discuss the option with their physician. This review will highlight the history of the vaccine, barriers to vaccination, current recommendations, and future directions for success.

1. Introduction

Human papillomavirus (HPV) is the most common viral infection of the reproductive tract, and persistent infection with high-risk types is associated with precancerous and cancerous lesions. Although HPV has been implicated in multiple cancers including cancers of the vulva, vagina, and oropharynx, its association with invasive cervical cancer is the most significant. Current estimations attribute greater than 90% of cervical cancers to high-risk HPV infection [1]. Cervical cancer continues to be a significant cause of morbidity and mortality worldwide, with the greatest burden of disease in low-income countries with limited access to both screening and HPV vaccination [2].

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Declaration of competing interest

SD: Grant/research support (Merck)

KM: none

WKH: Grant/research support (Merck) and Consultant (Pathovax)

Prophylactic HPV vaccination is a powerful strategy to reduce and eradicate HPV-related disease and cervical cancer. Long-term studies have demonstrated impressive efficacy, immunogenicity, and safety results. Despite overwhelming evidence regarding the reduction of HPV infection incidence, anogenital warts, and preinvasive disease in both vaccinated and unvaccinated populations [3], the implementation and uptake in both low and high-income countries continues to be challenging. Barriers to vaccination are multifactorial and include cost, infrastructure limitations and social stigma. The goal of this paper is to provide an update on current vaccine recommendations, challenges to vaccination, ongoing trials, and future directions.

Three prophylactic HPV vaccines are licensed for prevention of HPV-related disease: a bivalent HPV 16/18 vaccine, Cervarix (GlaxoSmithKline Biologicals, Belgium), a quadrivalent HPV 6/11/ 16/18 vaccine, Gardasil/Silgard (Merck & Co., USA/Sanofi Pasteur MSD, France); and a nonavalent HPV 6/11/16/18/31/33/45/52/58 vaccine, Gardasil9 (Merck & Co., USA). All three vaccines are composed of virus-like particles (VLPs), specifically L1, the major structural protein of the virion [4]. VLPs do not contain the viral DNA genome and are thus non-infectious and non-oncogenic. The vaccines differ in other key aspects: the bivalent vaccine uses baculovirus-infected *Trichoplusia* insect cell lines infected with L1 whereas the quadrivalent and nonavalent vaccines use a yeast cell type. In 2016, Merck and GlaxoSmithKline ceased distribution of their quadrivalent and bivalent vaccines, respectively, in the United States [5]. As a result, the nonavalent vaccine (9vHPV) is currently the only formulation available in the United States.

2. Vaccination recommendations and dosing

Since the introduction of the HPV vaccine in 2006, administration guidelines have undergone multiple updates regarding age, dosing schedule, and gender. Despite these changes, the basic tenet remains the same: prioritize immunization before initiation of sexual activity and subsequent exposure to HPV. The importance of immunizing males and females equally and the role for catch-up vaccination in late adolescent and adulthood has also been supported by subsequent research. The FDA indication for vaccination of boys was not approved until 2011, leading to a lag in vaccination rates. The importance of vaccinating males to decrease rates of cancer cannot be overstated, as the rates of HPV-related anal and oropharyngeal cancer are increasing [6].

The World Health Organization (WHO) currently endorses a 2-dose series for boys and girls aged 9e14 and a 3-dose schedule for those aged 15 years or older [7–9]. In the United States, the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommend vaccination for boys and girls aged 9e14 using a 2-dose schedule [10]. For those who do not receive the vaccine before after 15, vaccination is recommended in women aged 15e26 and men aged 15e21 in a three-dose series with an expanded recommendation for high risk subsets of men through age 26 [11,12]. However, ACIP members voted at their June 2019 meeting to expand the recommendation to all men up to age 26. This recommendation will be officially put into place once published in the CDC's Morbidity and Mortality Weekly Report (MMWR). In October of 2018, Merck was granted supplemental FDA approval to expand the range of eligible patients for the 9vHPV

vaccine to women and men from age 27 to 45 for the prevention of HPV-related cancers and diseases [13]. This approval came in response to the FUTURE III trial, which demonstrated a decreased risk of CIN, anogenital warts and persistent HPV infection in women age 24e45, even those with previous exposure to HPV, up to 6 years of follow-up after vaccination with the 4vHPV vaccine [14,15]. This expanded indication was also put to a vote at the June 2019 ACIP meeting, with members voting to recommend that individuals between ages 27 and 45 who have not yet been vaccinated discuss the option with their physician.

Dosing recommendations may continue to evolve as ongoing immunogenicity trials attempt to elucidate the ideal schedule. Just as the two-dose schedule recommendation amendment resulted from efficacy trials, new evidence suggests that even a single dose may confer a durable immunologic response. This is especially relevant in low-resource settings where the cervical cancer burden is high, and access to multiple doses of a vaccine is more difficult. Analyses of data from the Costa Rica Vaccine Trial (CVT) and PATRICIA trial have shown similar long-term protection against HPV infection in patients who received one versus three doses of the bivalent HPV vaccine [16].

Another unanswered question is the duration of the immune response to the vaccine and the potential indication for a vaccine booster. However, preliminary long-term studies demonstrate persistent vaccine effectiveness. Longitudinal data from the aforementioned CVT study shows 100% seropositivity against HPV 16/18 as well as an extremely low incidence of HPV 16/18 infection in vaccinated women at seven years in patients who received the bivalent vaccine [17]. Data from the FUTURE II trial reported by Kjaer et al. showed continued effectiveness of the quadrivalent vaccine, with no cases of CIN2p from vaccine-type HPV strains at 10 years of follow-up [18].

One question raised with the introduction of the 9vHPV vaccine, specifically for those who already received the 4vHPV is whether a role exists for re-vaccination to protect against the additional 5 HPV types covered by the 9vHPV. Garland et al. examined the immunogenicity effects in women given three doses of 9vHPV who had previously received three doses of 4vHPV. The results demonstrated that over 98% of vaccinees developed antibodies to all 5 additional types. A subsequent cross study comparison showed that the additional five type antibody titers were lower in those previously vaccinated with 4vHPV compared to those who received the 9vHPV, and the clinical significance of this is unknown. This same trial confirmed that the safety profile of 9vHPV given to HPV vaccine naive persons and 9vHPV given to persons who had previously completed a three-dose 4vHPV series were generally similar [19].

Although the above immunogenicity and safety data may be encouraging for re-vaccination, the general cost must be considered. In a cost-effectiveness analysis, Chesson et al. determined that the estimated cost per quality-adjusted life year (QALY) gained for giving an additional three doses of 9vHPV to females aged 13e18 years who have already received three doses of 4vHPV is over \$100,000. Additionally, the cost per QALY gained would be higher in females aged greater than 18 years and in males of any age with decreased benefit [20]. Currently, there are no formal recommendations by ACIP regarding re-vaccination and decisions must be made between patients and their providers on an individualized basis.

3. Vaccination rates

In an effort to increase vaccination rates in the US, 25 states have passed laws requiring funding for HPV education or HPV vaccination. Three states distribute free HPV vaccines through their health departments, and three have school-entry mandates including Virginia, Washington DC, and Rhode Island. In general, vaccination rates vary significantly between states with the highest in Washington, DC (78%) and lowest in Mississippi (29%) [21,22]. Nationwide HPV vaccination rates have increased in recent years, but remain lower than rates of other adolescent vaccines and below the Healthy People 2020 goal of 80% [23]. Based on the NIS-TEEN, rates of adolescents aged 13 to 17 who were up to date (receiving 2e3 doses based on age) with the HPV vaccine increased from 43.4% in 2016 to 48.6% in 2017 [21]. The rate of vaccination of at least one dose increased from 60.4% to 65.5%. Up to date vaccination rates in adolescent males continued to increase to 44.3% but still remain lower than in females, at 53.1% in 2017 (compared to 36.5% and 49.5% in males and females in 2016).

Differences in HPV vaccination were observed, as in previous years, based on race, socioeconomic status and geography, with notably higher rates of uptake in minority patients and those with lower socioeconomic status. Vaccination rates were highest amongst adolescents living below the federal poverty level, black and Hispanic compared to white adolescents, and those with Medicaid compared to private insurance. Given that these populations are disproportionately affected by cervical cancer and other HPV-related disease, this should be considered a great success of HPV vaccination access and promotion efforts. HPV vaccination may actually lead to strides in health equity that have not been achievable to this point, pending resultant decreases in HPV-mediated diseases. This concept has been coined by some authors as “reverse disparities” in HPV vaccination, highlighting the controversial nature of this vaccine, the disparate ways that parents and providers have interpreted recommendations and the general anti-vaccine sentiments nationwide amongst certain subgroups. An abstract presented at the 2019 SGO Annual Meeting showed a similar correlation between certain patient characteristics typically associated increased risk for cervical cancer and higher rates of vaccination by county in Alabama. The data demonstrated a positive correlation between high vaccination rates and poverty, rurality, high cervical cancer incidence and public insurance [24]. The association between rural/urban residence and vaccination rates warrants further study; however, as CDC data showed that those living in more urban Metropolitan Statistical Areas (MSAs) had higher rates of vaccination compared to those living in rural areas. A 2019 meta-analysis of vaccination rates reported in 118 studies also showed higher rates of HPV vaccination *initiation* but lower rates of series completion by black and Hispanic patients compared to whites [25].

4. Outcomes

As more time has passed since the introduction of the HPV vaccine, a growing body of literature has established its efficacy in reducing both genital warts and pre-invasive disease. Data on actual cancer rates are still in their infancy, given that the first vaccinated individuals are only now reaching an age at which cervical cancer would be expected to manifest. A 2018 Cochrane Review of 26 randomized controlled trials involving over 70,000 women and

girls summarized the efficacy and safety of bi- and quadrivalent HPV vaccines. Their comprehensive meta-analyses demonstrated no increase in adverse events compared to controls and significantly decreased risk of pre-invasive disease in young women [26,27]. Palmer et al. recently published a retrospective study of the national Scottish HPV vaccination and cervical cancer screening program including 138,692 women born between 1988 and 1996 [28]. The study compared rates of pre-invasive disease in vaccinated and unvaccinated women at age 20. The authors analyzed cervical cancer screening data from a cohort of unvaccinated women born in 1988 to women born in 1995e1996 who received the HPV vaccine between 12 and 13 years of age. Their data showed a significantly decreased rate of pre-invasive disease in the vaccinated group, with an 89% reduction in CIN3+, an 88% reduction in CIN2+, and a 79% reduction in CIN1+. A systematic review and meta-analysis published in *The Lancet* evaluated 65 articles examining the population-level impact of the HPV vaccine on girls and women, including 60 million individuals and eight years of follow-up. This study demonstrated the impact of HPV vaccine programs in high-income countries on the outcomes of HPV 16/18 infection (up to 83% reduction), anogenital warts (up to 67% reduction) and CIN2p (up to 51% reduction) [29]. These outcomes were most substantial and had the most herd effect when the HPV vaccine was rolled out in multiple age cohorts and at high rates, such as those in Australia, Denmark, New Zealand and Canada (Quebec).

In the United States, population-based data have also shown a decline in pre-invasive disease. McClung et al. compared rates of pre-invasive disease in 2008 and 2016 in the five CDC HPV Vaccine Impact Monitoring Project (HPV-IMPACT) sites e New Haven County Connecticut, Monroe County New York, Davidson County Tennessee, Alameda County California and portions of Washington and Multnomah Counties Oregon [30]. Overall number of CIN2p cases decreased from 216,000 in 2008 to 196,000 in 2016 per 100,000 women. The authors estimate that 76% of CIN2p cases were attributable to vaccine-specific HPV types. When stratified by age, rates of pre-invasive disease were highest in the 20–24 year-old group. Over time rates of CIN2p per 100,000 women decreased significantly in women aged 18e19 (206 to 12/100,000) and 20–24 years (559 to 151/100,000), but increased significantly in women aged 40–64 years. In addition to the impact that the HPV vaccine likely had on decreasing rates of pre-invasive disease in younger women, it is important to note that changes in cervical cancer screening practices including HPV co-testing may have impacted the sensitivity of detecting pre-invasive disease, contributing to the increased detection of CIN2p in older women. These results are compelling as it is likely that high-grade dysplasia rates will drop as HPV vaccination rates have continued to improve. Another analysis of the HPV-IMPACT data looking at adenocarcinoma in situ (AIS) showed a similar significant decrease in rates of AIS in women age 20e24 from 2008 to 2015, without a decrease in any older age groups [31]. Finally decreasing morbidity from anogenital warts is a significant impact of HPV vaccination. Decreases in incidence of anogenital warts of greater than 60% have been seen in countries with national HPV vaccination programs [3].

5. Future directions

In January 2019, Australian researchers made a bold statement that cervical cancer would be eliminated as a public health problem in their country in less than 20 years. This is based on projections of HPV vaccination rates and cervical cancer screening rates that show the incidence of cervical cancer will decrease to less than four cases per 100,000 women between 2021 and 2035, and that mortality of cervical cancer will decrease to less than one death per 100,000 women by 2034 [32]. These estimates assume vaccination with the 9vHPV vaccine and primary HPV screening. These provocative data are the result of robust nationwide HPV vaccination and cervical cancer screening programs, and their outcomes and predictions are promising and exciting. In the meantime, additional resources towards overcoming barriers and achieving similar results worldwide are necessary, many of which are already underway.

New prophylactic vaccines are under development. A novel trivalent HPV 16/18/58 vaccine is currently under development with promising non-inferiority results compared to the quadrivalent vaccine [33]. This vaccine is intended for the Asia-Pacific region which is disproportionately affected by HPV58. While rarely found elsewhere worldwide, HPV58 ranks third among HPV types associated with cervical cancer in South Korea, Japan, and China [33]. Additionally L2-based vaccines, such as the RG1-VLP vaccine, may provide a broader spectrum of HPV coverage and have the potential for a lower cost alternative to existing L1-based vaccines [34]. The RG1-VLP vaccine has shown robust antibody response in animal studies with as many as 21 high- and low-risk HPV types, and is currently being considered for Phase I trials.

Other trials are ongoing to address the efficacy of different dosing strategies and the long-term efficacy of the vaccine. We have seen a change to a more convenient dosing schedule for young adolescents based on data demonstrating the efficacy of two versus three doses of both the bivalent and quadrivalent vaccines for young adolescents [7,8]. This question is especially important given the cost and inconvenience of the multi-dose regimen. Post-hoc analyses of the Costa Rica Vaccine (CVT) and PATRICIA trials demonstrated single-dose efficacy for preventing high-risk HPV infection comparable to that of patients who received two or three doses [16]. To confirm these findings, the ESCUDDO trial aims to specifically compare a one-dose to a two-dose vaccine regimen of both the bivalent and 9vHPV vaccines administered to girls in Costa Rica.

Finally, while HPV vaccination rates are steadily increasing in the US, these rates vary substantially across geographic and sociodemographic parameters. In order for the US to achieve similar outcomes to our colleagues in Australia, public health professionals, cancer prevention advocates and providers will need to continue efforts to increase vaccination rates. Organizations like the National Cancer Institute, American Cancer Society and the CDC have put forth educational campaigns and funding and should continue these efforts until at the minimum, coverage for the HPV vaccine nears that of other adolescent vaccines such as Tdap and meningococcal.

Acknowledgement

WKH: His effort is supported by the National Institutes of Health (FUNDER: NIH; GRANT ID: P50 CA098252).

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HIGHLIGHTS

- The HPV vaccine has been proven to be safe and effective, supported by over a decade of research.
- Vaccine recommendations have undergone key changes regarding age, dosing schedule, and gender.
- Guidelines have recently expanded to include recommendations for all persons up to age 45.
- Higher rates of vaccine uptake are being seen in minority and lower socioeconomic status patients.
- Trials are ongoing to clarify ideal dosing schedules and the possibility of a one-dose vaccine.