EDITORIAL

HPV vaccination: Clinical potential, implementation challenges, and future directions

Rebecca B. Perkins

Department of Obstetrics and Gynecology, Boston University School of Medicine/Boston Medical Center, Boston, MA, USA

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Summary

Human papillomavirus (HPV) causes an estimated 700,000 cancer cases worldwide, including 530,000 cervical cancers, 22,000 oropharyngeal cancers, 24,000 anal, 21,000 vulvar and vaginal, and 11,000 penile cancers.¹ The search for an infectious cause of cervical cancer began in the 19th century, but the link to HPV was not discovered until the 20th century. In the 1970s, HPV 6 and HPV 11 were detected in laryngeal papillomas and condylomas. Over the next decade, Dr. Harald Zur Hausen and colleagues at the German Cancer Research Center isolated additional HPV strains from cervical cancers. Scientists found that HPV16 and 18 were the most common viral types isolated from cervical cancers from all geographic regions. In the 1990s, the development of today's HPV vaccines began. Early efforts were hampered by the lack of a cell culture system to produce HPV and an animal model to assess efficacy. The ability to overexpress the HPV capsid protein and generate virus-like particles (VLPs), which also are the technical basis for recombinant hepatitis B vaccine, provided a key breakthrough in HPV vaccine development. This effort was pioneered by Drs. Ian Frazer and Jian Zhou. The structure of HPV vaccines consists only of the outer viral protein shell without viral DNA, so VLPs are non-infectious.

HPV infections differ from many vaccine-preventable diseases because infection is local, not systemic, so the field was generally skeptical about the ability of a systemic vaccination to prevent disease. Yet clinical research showed that HPV virus-like particles containing viral L1 capsid proteins could elicit an immune response capable of preventing infection. HPV vaccines prevent close to 100% of infections with vaccine-type HPV strains among naïve subjects, with excellent persistence of long-term immunity, with the result that HPV dysplasias are prevented at a rate of close to 100%. In this regard, even though vaccination ultimately can prevent HPV-induced cancers, it is worth noting that HPV vaccine (like hepatitis B vaccine) is an infectious disease vaccine, not a cancer vaccine, in terms of its mechanism of action.

In this issue, we review the epidemiology of HPV-related cancers and the potential of currently-available vaccines to reduce disease. We also address some remaining questions and challenges. The field is still gathering the data needed to optimize dosing schedules, and lacks a definitive immune correlate of efficacy. Therapeutic vaccines may be on the horizon for

men and women currently suffering with HPV-related diseases. Yet the biggest challenge today lies in bringing current prophylactic vaccines to everyone in need. For reasons outlined in this Special issue, fewer adolescents receive HPV vaccines than other adolescent vaccines, resulting in suboptimal levels of disease prevention. Challenges addressed in this Special issue include parental attitudes and public perceptions that cause difficulties with HPV vaccine uptake utilization, and the critical role health-care providers play in educating parents. We also discuss the special catch-up population of men who have sex with men (MSM). Lastly, we consider ways to improve HPV vaccination rates through interventions within healthcare systems, school-located vaccine provision, legislation, and alternative venues.

Morbidity and mortality from HPV-induced cancers and potential impact of vaccines

We will not see the impact of current vaccinations on HPV-related cancer rates for decades, and prevention of cancer is neither an ethical nor a realistic endpoint for clinical efficacy trials, but existing data are extremely promising. HPV infections peak in the early twenties, and cancers usually occur in the fifth and sixth decades of life. Based on existing data regarding the prevalence of HPV16, 18, 31, 33, 45, 52 and 58 in cervical cancers, vaccine-induced prevention of infection should prevent up to 90% of cervical cancers if protection is complete and lifelong (Lockett, p 1332). Current screening regimens already reduce rates of invasive cervical cancers by up to 80%, but require intensive surveillance and invasive procedures to remove precancerous tissue. HPV vaccines have been shown in both clinical and population-level studies to reduce rates of cervical dysplasia, the precursor to invasive cervical cancer, and will be expected to reduce rates of both invasive testing and treatment as well as cancers (Lockett, p 1332).

HPV also causes up to 75% of oropharyngeal squamous cell carcinomas, whose incidence has more than doubled over the past 3 decades (Ward, p 1343). While HPV vaccination has not yet been proven to decrease rates of oropharyngeal cancers, 95% of HPV-related oropharyngeal cancers are caused by HPV16, and clinical trial data indicate that the bivalent vaccine (2vHPV) is 93% effective at preventing oral HPV16 infections.

Thus HPV vaccines should be expected to provide immunity against these oral cancers if protection is complete and lifelong (Ward, p 1343). The incidence of squamous cell cancer of the anus also has more than doubled over the past 4 decades, and is more common among women than men (Stier, p 1348). The populations at the highest risk for anal cancers include HIV⁺ men and women, MSM, women with a history of cervical cancer, and immunosuppressed patients. The quadrivalent vaccine (4vHPV) has been effective in preventing not only anal HPV infections, but also anal intraepithelial neoplasia grades 2–3 in young men. HPV vaccines also decrease the risk of recurrence of anal intraepithelial neoplasia in MSM following treatment (Stier, p 1348). Vulvar cancer is also rising in incidence; rates of pre-invasive disease have quadrupled over the past 4 decades (Buchanan, p 1352). The 9vHPV vaccine should protect against 87% of vulvar cancers if protection is complete and lifelong (Buchanan, p 1352).

Because genital warts occur within months of HPV infection, the largest amount of population-level vaccine effectiveness data exist for prevention of genital warts. All studies show that higher vaccination coverage within populations correlates with decreasing incidence of genital warts, and herd immunity is observed when coverage rates are high (Wangu, p 1357). HPV vaccination also has the potential to reduce or eliminate recurrent respiratory papillomatosis (RRP), a debilitating disease primarily of childhood caused by HPV6 and 11 (Wangu, p 1357). Cost-effectiveness analyses, which assume lifelong protection, indicate that switching from 4vHPV to 9vHPV can save \$386 million (US) and gain 147,000 QALYs. Therefore, despite the \$13 (US) difference in cost per dose between the 4vHPV and 9vHPV vaccines, using the latter should be cost-saving (Chesson, p 1363).

Several questions remain regarding the impact of current vaccines on rates of HPV-related cancers. If the vaccines function as expected, cancer rates will begin to drop over the next several decades. Vaccination should have the greatest impact in reducing rates of cancers for which no screening recommendations exist: oropharyngeal, anal, vulvar, vaginal, and penile. The greatest reduction in cervical cancer rates would be expected in low- to middle-income countries that lack comprehensive screening systems. However, realization of vaccine potential will take decades, and is dependent on lifelong immune protection, thus continued vigilance is necessary. In the case of cervical cancer, continued screening will be crucial to continue to prevent invasive cancers for the next several decades (Lockett, p 1373), and vaccinated women must understand that cervical cancer screening is still recommended (Higgins, p 1498).

Clinical experience and implications

Benefits and remaining questions around a 2-dose series vs. the standard 3-dose series

A two-dose series for HPV vaccination has been implemented by several countries worldwide, and is under consideration in the US. The purported benefits of a 2-dose schedule are reduced costs and easier logistics. These benefits are important, but are not guaranteed. Vaccine manufacturers' current practice often involves charging by completed schedule, not by

dose, thus the price per dose increases and the total vaccine cost per child vaccinated remains similar regardless of whether a 2- or 3-dose schedule is used. This might limit saving to administration costs only. Increased compliance with 2- compared to 3-dose schedules is also not guaranteed. No-show rates for medical visits increase as the time between visits increases,² so moving from a 3-dose schedule with 2 to 4 months between doses to a 2-dose schedule with 6 to 12 months between doses may not have the desired impact on completion rates. Cloessner et al. (p 1375) found that if US adolescents who had received 2 doses given at least 6 months apart were considered fully protected, rates of complete vaccination would improve only 4%. However, long intervals are not the current recommendation, so the effect of implementing 6- to 12-month dosing intervals remains unknown.

Equivalent efficacy between 2- and 3-dose schedules has not yet been proven. Immunogenicity data show that vaccination at 0 and 6 months in girls and boys ages 9–14 elicits antibody responses similar to those by the standard 0-2-6 month dosing schedule in young adults aged 15 and older (Donken, p 1381; Basu, p 1394). However, determining immunologic correlates of protection for HPV vaccination is more complicated than for many other vaccines. Serum antibody levels do not appear to correlate with protection, and antibody secretion does not explain the prevention of HPV-related non-mucosal lesions, such as vulvar dysplasia (Turner, p 1403). Thus data on clinical outcomes are important. No studies to date compare virological and disease endpoints between boys and girls aged 9–14 receiving 2 vs. 3 doses. Most existing outcome studies use ecological data and thus suffer from flaws including age over 15 at receipt of 2 doses and insufficient dosing intervals to create immune memory. However, nearly all studies indicate a dose-response effect, with 3 doses being more effective than 2 doses for the prevention of persistent infection, genital warts, and cervical dysplasia (Donken, p 1381; Basu, p 1394). Additional follow-up from existing studies as well as additional randomized data with clinical endpoints are necessary to determine whether alternative schedules provide protection for at least 10 years following vaccination (Basu, p 1394).

HPV vaccine safety

All studies to date indicate that 4vHPV is safe and well-tolerated. Large population-based studies designed to find rare side effects, including venous thromboembolic disease, autoimmune disease, central nervous system and demyelinating diseases have shown excellent vaccine safety (Gee, p 1406). Data on 9vHPV safety are limited to clinical trials, but the side-effect profile seems similar to that of 4vHPV. Plans for continued monitoring of 9vHPV include the Vaccine Adverse Events Reporting System, Vaccine Safety Datalink, and the FDA sentinel system (Gee, p 1406). Overall, side effects are uncommon and serious vaccine-associated serious adverse events are very rare, which means that the risk-benefit ratio of vaccination is overwhelmingly positive.

Therapeutic HPV vaccination

Prophylactic HPV vaccines have no effect on existing HPV-related cancers, given that their mechanism of action is the induction of virus-neutralizing antibodies that prevent initial

HPV infection but have no effect on HPV inside infected cells. At least 50% of men and women over age 18 are estimated to have contracted an HPV infection, which would translate to a substantial portion of the world's population at risk for HPV-related cancers. Therefore, therapeutic vaccines are being explored. Immunotherapies for the treatment of HPV-related cancer or pre-cancer infections focus on generating cellular immune responses against viral antigens associated with cellular transformation, most commonly E6 and E7. Therapies include combinations of therapeutic vaccines and/or immunomodulators. Protein and peptide vaccines, while promising, have not yet demonstrated effectiveness in human clinical trials. Viral-vectored vaccines have had more promising effects. DNA vaccines coupled with electroporation increased cervical dysplasia clearance over placebo, and may have promise for future therapies. Cell-based therapies involve isolating and manipulating immune cells ex-vivo prior to returning them to the patient. The most promising of these is the expansion of autologous, antigen-specific cytotoxic T-lymphocytes, which demonstrated some effectiveness against cancers and is the focus of an ongoing clinical trial. The goal of non-specific immunostimulants is to overcome the mechanisms tumor cells use to evade the immune system. The benefit of this less specific approach is the applicability of drugs to more than one tumor type, for which several clinical trials are ongoing (Skeate, p 1418).

Attitudes, perceptions, and communication around HPV vaccines

Communication around fostering vaccination can be complex, and HPV vaccination has presented exceptional challenges due to high levels of media controversy and its association with sexuality. Media coverage plays an important role in both public perception and public policy related to vaccination given that many people obtain their information from the media and politicians may consider news attention to reflect constituent concerns (Gollust, p 1430). Initial media coverage of HPV vaccination was generally positive and focused on cancer prevention as a breakthrough, but also raised concerns related to cost, safety, and promoting promiscuity. When states began considering mandates, many under the influence of heavy lobbying from the pharmaceutical industry, media reports began focusing on conflict and controversy. Most recent articles have focused on politics and ideological concerns rather than health messages. Notably, male vaccination has received little media attention, which may contribute to lack of public awareness around the recommendation for male vaccination (Gollust, p 1430). Despite persistent media coverage relating to vaccination of women and highly publicized concerns related to promoting promiscuity among vaccinated girls, reviews of sexual behavior following vaccination have shown this to be profoundly untrue, with vaccinated girls practicing either equivalent or safer sexual behaviors compared to unvaccinated girls (Kasting, p 1435; Hansen, p 1451).

Provider recommendation is one of the most important predictors of HPV vaccine series initiation, but many providers are using ineffective messaging: failing to strongly endorse vaccination, presenting HPV vaccination separately from other

recommended adolescent vaccinations, and presenting vaccination as an 'optional' vaccine that can be delayed (Gilkey, p 1454). Strong recommendations are associated with higher HPV vaccine acceptance (Dempsey, p 1469), but HPV vaccination is less likely to be strongly recommended than other adolescent vaccines (Gilkey, p 1454). Low-quality communication between providers and parents results in lower vaccination rates, and groups with the highest risk of cervical cancer might benefit most from improvements in provider-parent communication (Moss, p 1476). Paradoxically, more highly educated parents tend to report higher quality communication, but also have higher levels of vaccine hesitancy (Gilbert, p 1484). Among adolescents however, education level does not predict vaccination. Rather, provider recommendation and the understanding that the intent of vaccination is cancer prevention correlate with vaccination (Suryadevara, p 1491).

Knowledge gaps exist, especially among males (Napolitano, p 1504). Ineffective communication is more likely when providers are recommending vaccination for males (Malo, p 1511). As a result, parents of boys are more likely than parents of girls to state that the reason they had not vaccinated their adolescent was the lack of a provider recommendation (Lindley, p 1519). Ineffective communication may also contribute to failure to complete the vaccine series. Few medical practices have reminder and recall systems for adolescent vaccines, and therefore rely on patients to schedule the second and third doses. Patients, however, are often expecting providers to schedule needed appointments, and mismatched expectations are a common cause of failure to complete the series (Perkins, p 1528).

Vaccinating all boys and girls in early adolescence would be most effective for reducing population-wide levels of HPV diseases. However, certain young adult populations bear a disproportionate burden of disease and deserve special mention. MSM have higher rates of HPV infection and HPV-related cancers, and do not benefit from herd immunity related to vaccinating females. Studies among MSM indicate high levels of vaccine acceptance as long as out-of-pocket costs are low, but also indicate limited understanding of the role of HPV in male cancers (Sadler, p 1536; Giuliani, p 1542; Zou, p 1551). The Quebec Immunization Committee recommends vaccination of both male and female pre-adolescents as the most effective way to prevent HPV-related diseases, along with targeted catch-up vaccination for MSM through age 26 (Sauvageau, p 1560).

Tools for improving HPV vaccine coverage

Evidence-based interventions

Several studies have examined which interventions appear to be most effective for improving HPV vaccination rates. Healthcare system based interventions generally showed positive effects, while public education campaigns alone failed to substantially improve coverage rates (Smulian, p 1566). Overall, programs focusing on provider assessment and feedback interventions improved initiation more than completion, while patient reminder and recall programs improved completion more than initiation (Oliver, p 1589). All types of patient reminders were effective, including texts, letters, and phone calls (Smulian, p 1566; Oliver, p 1589). Educational videos and patient navigators also improved vaccine coverage in

small studies (Smulian, p 1566). Interestingly, 3 out of 4 practices that evaluated the net effects of reminder/recall programs on practice revenue demonstrated an overall increase in revenue generated by the additional visits that outweighed the costs of the programs. Provider-targeted interventions were more heterogeneous in impact, with limited effectiveness for provider reminders and the best results seen for multi-component programs (Smulian, p 1566; Oliver, p 1589). In contrast, reducing out-of-pocket costs to patients did not improve vaccination rates (Smulian, p 1566). Overall, the interventions outlined by the Community Preventive Service Task Force for increasing appropriate vaccination can be applied to HPV vaccination, although the magnitude of improvement may be slightly lower for HPV vaccines than for other childhood vaccines (Oliver, p 1589).

School-located vaccination

Schools present opportunities as well as challenges for raising vaccination coverage. School-located immunization has been used to achieve high levels of HPV vaccine coverage in Canada, Europe, and Australia, and school-located initiatives have previously been used successfully in the US to rapidly raise population coverage with polio and hepatitis B vaccines (Palfrey, p 1594; Middleman, p 1599). School-located programs that have been introduced on a small scale have shown high levels of series initiation and completion, as have programs in school-based health centers (Smulian, p 1566; Middleman, p 1599). Many US parents support the creation of school-located immunization programs, citing convenience and improved access. Some, however, have voiced concerns over the qualifications of school nurses to administer such programs (Vercruysse, p 1606; Middleman, p 1599). School-located programs can be cost-effective ways to reach the majority of students, although financial reimbursement for vaccines can be challenging in the absence of provision by a single payer (Middleman, p 1599). If school-located immunizations are developed in the future, ensuring that all recommended vaccines are included is critical to program success (Middleman, p 1599).

Policy and legislative options

Public policy and legislation also present opportunities and challenges. School-entry requirements, or mandates, have been credited with successfully raising coverage rates of childhood and adolescent vaccines. Small increases in HPV vaccination coverage have been noted in states that have enacted mandates for other adolescent vaccines (Smulian, p 1566). However, school-entry requirements for HPV vaccination and mandated vaccine education have failed to improve HPV vaccination rates to date (Perkins, p 1615; Smulian, p 1566). Attempts to pass legislation are often met with intense resistance that weakens or derails proposed actions (Brandt, p 1623). In the cases of Virginia and Washington DC, HPV vaccine mandate legislation was enacted with liberal opt-out clauses that do not apply to other vaccines, which weakened the impact of the legislation (Perkins, p 1615). Even parents and providers who favor HPV vaccination report only limited support for school entry requirements primarily due to concerns over limiting parental autonomy or provoking public backlash (Vercruysse, p 1606; Califano, p 1626). Thus, some providers support requirements if opt-outs are allowed,

although these provisions limit the effectiveness of the legislation (Califano, p 1626).

Rhode Island, however, may provide an example of the successful implementation of school-entry requirements. In August 2015, Rhode Island implemented a school entry requirement without special exemptions. Rhode Island has several unique qualities that facilitate HPV vaccine requirements. First, HPV vaccines are universally distributed by the state, removing financial obstacles to patients and providers. Second, Rhode Island maintains a robust immunization registry, which simplifies tracking administered doses. Third, school-entry requirements were implemented following initiation of a comprehensive program involving personalized education and feedback given to all 180 pediatric practices in the state, and the establishment of a public education campaign, *Vaccinate Before You Graduate*. In this setting, preliminary results are favorable, with a reported 73% of 7th graders initiating the series as of autumn 2015 (Washburn, p 1633).

Alternative venues

In addition to schools, other venues also may be opportunities for providing vaccination, especially for catch-up populations and series completion. Reproductive care providers, such as family planning centers, may be important sites for catch-up vaccination for young women (Dorton, p 1639). In addition, pharmacies have been proposed as partners in providing HPV as well as other vaccinations (Brandt, p 1623; Rothholz, p 1646). Forty-nine states and territories allow pharmacists to administer HPV vaccination, although many have age restrictions or other requirements. Strategic collaborative relationships between physicians and pharmacists could expand access to vaccination by creating an “immunization neighborhood” that gives patients expanded and more convenient access. Work remains to be done in this area, especially for ensuring adequate documentation and communication between healthcare facilities and pharmacies. Any new policies must also guarantee that uninsured and under-insured patients have access to vaccination at commercial pharmacies, so that these policies decrease, rather than exacerbate, disparities related to healthcare access.

Conclusion: Areas for future research

Many human cancers are caused by infectious agents, including cancers of the liver, stomach, nasopharynx, and bladder, among others. Advances in medicine have allowed the prevention or treatment of many of these cancers including vaccination against hepatitis B, and testing for and treatment of *H. pylori* and *Schistosoma* infections. HPV is one of the most virulent carcinogenic agents, causing over 700,000 cervical, oropharyngeal, anal, vulvar, vaginal and penile cancers each year.

HPV vaccination has incredible potential to sharply reduce the numbers of these cancers, but questions remain. One crucial knowledge gap is the lack of understanding of the mechanisms by which HPV vaccination prevents infection, and the development of assays that accurately reflect immunity. Because HPV infections continue to be acquired throughout life, decades of protection are required to prevent cancers. However, current immunologic assays do not accurately predict susceptibility to infection, and are thus insufficient to measure

if and when booster doses might be required. Prospective registries exist in the US and worldwide to follow vaccinated women for the development of clinical disease, and these are crucial to understanding the duration of infection provided by vaccination. However, the development of clinical disease may occur many years after infection, and also depends on other factors including risk of disease exposure, thus the information from these registries are critical but imperfect measures of immunity. The development of registries that include men will also be important to demonstrate long-lasting protection against HPV-induced diseases in men.

Understanding how age at vaccination and the number and timing of doses affects rates of persistent infection, genital warts, and cervical and anal dysplasia will also be an important next step in HPV vaccination research. Both randomized controlled trials and prospective cohort studies with long-term follow-up of at least 10–15 years are necessary to feel confident that vaccination at ages 11–12 will protect adolescents through their early twenties, when they are at the highest risk of HPV exposure, and whether a booster dose is needed, as is the case for some other vaccines. Because millions of people are already exposed and therefore at risk for HPV-related cancers, research into cancer screening and therapeutic vaccination must also continue.

While questions remain, we do know that HPV vaccines are safe and effective, but not reaching enough people. Additional research and public health work is needed to ensure that all adolescents for whom HPV vaccines are recommended receive vaccination. Education for providers and the public should continue to emphasize vaccine effectiveness and safety, and the importance of vaccination in preventing cancers in both men and women. Research on addressing and overcoming parental

hesitation toward vaccines in general, and HPV vaccine in particular, remain important for safeguarding children's health. Geographic disparities exist, both in the US and worldwide, that will exacerbate cervical cancer disparities if not addressed. US states with high cervical cancer rates and low- and middle-income countries that lack comprehensive screening programs also have low vaccination rates or limited access to vaccination. Improved public health outreach within the US, and international work supporting very-low-cost vaccination in low income countries, such as that supported by GAVI (Global Vaccine Alliance) and others should be public health foci for the future.

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No potential conflicts of interest were disclosed.

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References

- [1] Forman D, de Martel C, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L, Vignat J, Ferlay J, Bray F, Plummer M, Franceschi S. Global burden of human papillomavirus and related diseases. *Vaccine* 2012; 30 (Suppl 5):F12-23; PMID:23199955; <http://dx.doi.org/10.1016/j.vaccine.2012.07.055>
- [2] Norris JB, Kumar C, Chand S, Moskowitz H, Shade SA, Willis DR. An empirical investigation into factors affecting patient cancellations and no-shows at outpatient clinics. *Decis Support Syst* 2014; 57(1):428-43; <http://dx.doi.org/10.1016/j.dss.2012.10.048>