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REVIEW

Update on human papillomavirus vaccination: Where are we now?

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Abstract

Infection with human papillomavirus (HPV) is the major cause of pre-invasive and invasive lesions of the urogenital tract, resulting in morbidity and mortality worldwide. HPV-related infection is responsible for most cases of cervical cancer, a leading cause of cancer death in women worldwide. Developed countries have screening programs in place to detect precancerous lesions at early stages; in resource-limited settings however, HPV related diseases are often identified in advanced stages. This is due to limitations in the availability and roll out of effective screening programs. The relatively recent availability of the HPV vaccine has provided a new public health opportunity to decrease the incidence of HPV-related disease. The high mortality rates seen in developing countries could be reduced through effective implementation of HPV vaccination programs. Large trials have proven the efficacy of bivalent, quadrivalent vaccine and most recently 9-valent vaccine. Uptake in vaccination remains low due to multiple barriers including lack of education, lack of access, and costs. New strategies are being assessed to increase access, increase knowledge and reduce costs that may result in feasible vaccination programs worldwide. The goal of this article is to review the effectiveness and safety of the current HPV vaccines available, vaccine delivery strategies, cost effectiveness, and efforts to improve the acceptability. A literature search was conducted through PubMed using the terms "HPV vaccination, and safety, and males, and acceptability and strategies, and cost effectiveness," focusing on articles published between 2006 and 2015. The most relevant and larger scale trials were evaluated for discussion.

Key words: Human papillomavirus; Vaccines; Cervical cancer; Cancer prevention; Public health

Core tip: Human papilloma virus (HPV) represents the major cause of pre-invasive and invasive lesions of the urogenital tract. This article will review the efficacy, safety and approval of the currently available vaccines against HPV including the bivalent, quadrivalent and nine-valent vaccines. Indications for use in men, immunocompromised individuals and older cohorts will also be discussed. Additionally a summary of worldwide vaccination practices, cost effectiveness, vaccination and methods to improve vaccination uptake and acceptance will be reviewed.

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INTRODUCTION

Worldwide, cervical cancer is the fourth most frequent cancer in women affecting almost 500000 women each year and is the most common cause of cancer death among women in developing countries[1]. About 70% of the global burden falls in areas with low resources including sub-Saharan African countries[1]. Infection by certain types of human papillomavirus (HPV) is required for almost all cases of cervical cancer. HPV is the most commonly sexually transmitted infection not only in the United States but worldwide[1,2].

In the United States, 79 million people are currently infected with HPV and 14 million people are newly infected each year. Additionally, 26000 of all new oral and urogenital related cancers are attributed to HPV annually, of which approximately 17000 are in women and approximately 9000 are in men[2]. More than 4000 women die of cervical cancer each year in the United States, and as many as 93% of these cancers could be prevented by screening and HPV vaccination[3].

Infection with HPV is implicated in the development of not only cervical cancer, but also many other cancers including anal, vaginal, vulvar, penile, oropharyngeal carcinomas and oral cancers. HPVs are a family of deoxyribonucleic acid (DNA) viruses that infect skin or mucosal cells. There are over 100 types of HPV and > 40 types infect the anogenital tract. At least 13 types are considered oncogenic (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68)[1,2].

Universal access to HPV vaccination, screening and treatment services are crucial in reducing the overall burden of HPV related diseases. The incidence and mortality from cervical cancer has not decreased as significantly in developing countries as it has in the United States following the introduction of the Papanicolaou smear[4]. There are many obstacles to screening, generally attributed to a lack of infrastructure and resources, as a result of technical, medical and financial constraints[4]. Lack of awareness and education among women and health care providers have also been reported to play a role[4]. Therefore a critical public health need is being addressed with the introduction of HPV vaccines as a major strategy for the prevention of not only cervical cancer but all HPV-related diseases.

The objective of this article is to review updated information regarding HPV vaccine approval, availability and safety, review the major trials of bivalent, quadrivalent and 9-valent vaccines, discuss implementation concerns including vaccine delivery strategies, cost-effectiveness of HPV vaccination and efforts to improve vaccine acceptability worldwide.

DISCUSSION

Vaccine development and rationale

Given the endemic nature of HPV infection, attempts have been made at the prevention of HPV-related sequelae such as high-grade cervical lesions and deaths due to cervical cancer with the introduction of HPV vaccines. The lifetime risk of genital infection with an oncogenic strain of HPV is thought to be greater than 80%, however in immunocompetent individuals 90% of infections become undetectable without intervention[5]. The risk of developing squamous cell carcinoma of the cervix is approximately 400 times higher following infection with HPV-16 and 250 times higher following infection with HPV-18 as compared to those not infected. HPV types 16, 18, 31, 33, 45, 52, and 58 account for approximately 90% of all HPV positive squamous cell carcinomas[1]. Wagner *et al*[6] reviewed publications investigating the genotype-specific prevalence of HPV-related cervical, vulvar and vaginal disease in women worldwide. Based on the results of these studies, HPV genotypes 16, 18, 31, 33, 45, 52, 58 are responsible for 90% of all cervical cancers providing rationale for the utilization of the 9-valent L1 VLP vaccine (9vHPV) vaccine. However, a lack of data regarding genotype-specific prevalence exists in several regions of the world with the highest age-standardized incidences rates of cervical cancer[6]. A study by Clifford *et al*[7] examined the global prevalence of HPV types in cytologically normal women. Their findings demonstrate heterogeneity in the distribution of HPV types globally. Although HPV 16 prevalence is higher in sub-Saharan Africa than Europe, these women are less likely to be infected with HPV 16 than European women[7]. Additionally, HPV 35, 45, 52, 56, and 58 (other high-risk types) and low-risk types were more prevalent in women with HPV infection in sub-Saharan Africa[7]. While this study is limited in representation of sub-Saharan countries (n = 1), it addresses the need for prevalence-specific screening and vaccination with vaccine choice (quadrivalent, bivalent, or 9-valent) tailored to regional HPV prevalence.

Much like vaccination for other communicable diseases, administration of HPV vaccines in HPV-naïve individuals attempts to provide herd-immunity for

Table 1 Phase III efficacy in women

	Future I	Future II	Patricia	CVT	Broad spectrum HPV vaccine study
Vaccine	Gardasil®	Gardasil®	Cervarix®	Cervarix®	Gardasil9®
Funding	Merck and Co., Inc.	Merck and Co., Inc.	GlaxoSmithKline	National Cancer Inst.	Merck and Co., Inc.
Number enrolled	6463	12167	18729	7466	14215
Number of countries	16	13	14	1	14
Duration of trial	4 yr	4 yr	4 yr	4 yr	4 yr
Age (yr)	16-24	15-26	15-25	18-25	
Lifetime sexual partners	< 4	< 4	< 6	No restriction	< 4
Exclusions	Pregnancy, history of abnormal Pap smear or genital warts	Pregnancy, history of abnormal Pap smear	Pregnancy, breastfeeding, history of colposcopy, autoimmune disease/ immunodeficiency, HPV 16/18-associated CIN2+ at enrollment	Pregnancy, breastfeeding, history of immunosuppression, hysterectomy, hepatitis A vaccination	Prior abnormal Pap smear, > 4 lifetime sexual partners, no prior abnormal finding on cervical biopsy
Primary endpoint	Incidence of vaccine-type HPV associated CIN1-3, AIS or cancer, combined incidence of vaccine-type HPV associated anogenital warts, VIN/VaIN1-3 or cancer	HPV 16 or 18 associated CIN2/3	Incidence of HPV 16 or 18 CIN2 or greater	HPV 16 or 18 persistent infection (12 mos.) or HPV 16 or 18 associated CIN2+	High-grade cervical, vulvar, and vaginal disease
Mean follow-up time	3 yr	3 yr	14.8 mo		
Immunogenicity	99.5% seroconversion after 3 doses	99% seroconversion to vaccine-associated HPV types	99.5% seroconversion rates in women aged 15-25 yr		Non-inferior to quadrivalent vaccine

CVT: Costa Rica HPV Vaccine Trials; HPV: Human papillomavirus; VIN/VaIN: Vulvar/vaginal intraepithelial neoplasia.

future generations and thus lower the burden of HPV-related disease. The median time from HPV infection to seroconversion is approximately 8-12 mo, however because HPV infection is restricted to the intraepithelial layer of the mucosa it does not induce a strong immune response[1]. Failure to develop a sufficient cell-mediated immune response leads to persistent infection and increased risk of progression to CIN 2 to 3[1]. The most type-specific HPV antibodies are directed against the L1 HPV viral protein providing a target for vaccine development.

Vaccine efficacy and safety

To date, two vaccines (bivalent and quadrivalent) against HPV have been approved for use in over 100 countries for the prevention of HPV-related disease.

Both vaccines are composed of non-infectious virus-like particles (VLPs) The quadrivalent vaccine (Gardasil®) targets HPV 6, 11, 16, 18, aimed at prevention of the two most oncogenic HPV types (types 16 and 18) which cause > 70% of cervical cancer worldwide, and types 6 and 11 which are responsible for approximately 90% of genital warts[8]. The bivalent vaccine (Cervarix®) contains purified viral proteins of HPV types 16 and 18, targeting only the oncogenic subtypes[1]. In the United States, the quadrivalent vaccine is administered on a 3-dose schedule (0, 2, and 6 mo), however in other countries, it is approved for a 2-dose schedule for girls and boys aged 9-13 years. The bivalent vaccine is given on a 2-dose schedule for boys and girls aged 9-14 years. Those > 15 years should receive a 3-dose schedule[1].

Efficacy: Four Phase Ⅲ efficacy trials were performed for the quadrivalent and bivalent HPV vaccines. These studies were designed to demonstrate efficacy in preventing incident vaccine-related HPV infection and preneoplastic lesions caused by incident persistent infections related to the subtypes of HPV in vaccines. The FUTURE Ⅰ and FUTURE Ⅱ trials evaluated Gardasil® while the PATRICIA and Costa Rica HPV Vaccine Trials (CVT) evaluated Cervarix®. All of the trials were large, blinded, and randomized controlled trials of young women (mean age 20). With the exception of the CVT, all studies were company-sponsored and multicenter involving multiple trial sites globally[9].

The FUTURE Ⅱ and PATRICIA trials used a precancer primary endpoint of cervical intraepithelial neoplasia (CIN) 2/3, adenocarcinoma in situ, or cervical cancer associated with HPV 16/18. FUTURE Ⅰ had an additional endpoint of HPV6/11/16/18-associated CIN1+ and external genital lesions including vulvar/vaginal intraepithelial neoplasia (VIN/VaIN). Among the trials, the median age at enrollment ranged from 15-26 years. Clinical trial details are described in Table 1 with an overall vaccine efficacy of > 99% between 14 mo and 3 years of follow up[9-13] (Table 1).

Many genotypes exist of both oncogenic (high risk) and genital wart causing (low risk) HPV. Partial cross-protection against non-vaccine oncogenic HPV types has been reported, however the clinical relevance is undetermined. While HPV types 16 and 18 are respon-

sible for 70% of global cervical cancer, oncogenic HPV types 31, 33, 45, 52, and 58 cause approximately 20% additional cervical cancer cases. A 9vHPV vaccine containing HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58 has the potential to prevent up to 90% of all cervical cancers globally[14].

The Broad Spectrum HPV Vaccine Study conducted a large Phase II/III clinical trial to assess efficacy, immunogenicity, and safety of the 9vHPV vaccine. The endpoints of this trial were to prove non-inferiority of anti-HPV 6/11/16/18 antibody response, and superior efficacy in HPV 31/33/45/52/58-related clinical outcomes for the 9vHPV vaccine as compared to the quadrivalent vaccine. In addition, a non-inferiority assessment was conducted assessing the percent risk reduction for 9vHPV *vs* quadrivalent vaccine[14].

Results showed that 9vHPV vaccine was efficacious in preventing high-grade cervical, vulvar and vaginal disease related to the 5 new HPV subtypes. Additionally the 9vHPV vaccine generated a non-inferior antibody response to HPV 6/11/16/18 as compared to the quadrivalent vaccine[14,15]. The United States FDA licensed the 9vHPV vaccine for use in 2014 under the name Gardasil®9[14].

Studies have been evaluated to determine potential benefit of 9vHPV vaccine in the United States and abroad. A population-based evaluation of the subtypes of HPV in women with CIN2+ was performed in the United States. Approximately 50% of lesions were attributable to HPV 16/18, while 25% of lesions were attributable to HPV 31/33/45/52/58. Older women and racial/ethnic minorities with $CIN2^+$ diagnosed were more likely to have subtypes other than HPV 16/18[16] and would potentially benefit from the extended coverage. Serrano *et al*[17] conducted a study evaluating the potential impact of the 9vHPV vaccine on cervical cancer prevention in 4 countries (Brazil, Mexico, India and China). Based on the proportion of invasive cervical cancers attributable to HPV types 31/33/45/52/58, they estimated an increase in prevention of invasive cervical cancer by 12%-19% across the 4 countries[17]. This represents a potential target for significant decrease in HPV-related cancers worldwide if adopted into use globally.

Safety: Multiple studies[18-20] have established the safety of the 2 major HPV vaccines currently approved. A large post-licensure trial was performed evaluating the safety of the quadrivalent vaccine among females aged 9-26 years which revealed no significant increased risk of Guillan-Barré Syndrome, stroke, venous thromboembolism, appendicitis, seizures, syncope, allergic reaction or anaphylaxis[18]. A study evaluating post vaccination risk intervals in females revealed same-day syncope and skin infections at the site of vaccination as the only risks associated with recent vaccination[19]. A study performed in Australia of > 380000 doses of quadrivalent HPV vaccine given in school-aged girls identified 35 possible hypersensitivity reactions to the vaccine. Further evaluation of these 35 individuals revealed only 3 cases of true hypersensitivity reactions and most individuals tolerated subsequent doses of vaccine[20].

Vaccine approval

In the United States, Gardasil® is approved for females only between ages 9-26 while Cervarix® carries FDA approval for women ages 9-25. In countries such as Canada and Australia, the HPV vaccines are currently licensed for use in women up to age 45[21]. In Australia, the quadrivalent vaccine was added to the National Immunisation Program in 2007 and the bivalent vaccine added in 2008[22]. The VIVIANE study, a Phase 3 multinational, double-blind, randomized controlled trial is currently underway to evaluate the efficacy, safety and immunogenicity of the Cervarix® vaccine in women older than 25 years. Enrollment was stratified by age into 3 groups. The primary endpoint was vaccine efficacy against 6-mo persistent infection or CIN1+ associated with HPV 16/18. Interim analysis found significant vaccine efficacy against the primary combined endpoint overall and specifically in the 26-35 and 36-45 year age groups[21]. A study conducted in Germany and Poland assessed the immunogenicity of Cervarix® in women aged 15-55. Schwarz *et al*[23] evaluated immune responses in serum and cervicovaginal secretions 6 years after the first dose of vaccine in women ages 15-25, 26-45, and 46-55 years who received 3 doses of vaccine. After 6 years all women across all age groups were seropositive for HPV 16 and > 97% were seropositive for HPV 18 indicating a sustained immune response regardless of age at administration[23].

Interim data from the VIVIANE study establishes safety and efficacy in preventing primary acquisition of target HPV at any age[21], while Schwarz *et al*[23] demonstrate equivalent immunogenicity in all age groups; however issues addressing cost-effectiveness still need to be addressed in order to best use resources to achieve the maximum benefit to the population. The optimal target range for intervention likely still remains in women ages 9-26, however future studies using 9vHPV vaccine may prove cost effective in preventing invasive cervical cancer in the older populations with the addition of HPV types 31/33/45/52/58.

HPV vaccination of males: HPV infection is most well known for causing cervical cancer in women; however it is also responsible for other cancers, some of which are in men. In 2002, while nearly 100% of the 492800 cervical cancers were attributable to HPV, 90% of anal cancers, 40% of penile cancers, 12% oropharyngeal cancers and 3% of the mouth cancers worldwide were attributable to HPV infection[24]. HPV infection with non-oncogenic strains 6 and 11 can also cause genital warts which affect both men and women. Thus, men can also benefit from vaccination with the HPV vaccine, both to decrease their rates of cancer and genital warts, and to decrease their transmission of the virus to their male

and female partners.

Efficacy of the quadrivalent vaccine in males was established in a study by Giuliano *et al*[25]. A randomized, placebo-controlled, double-blind multi-center trial was conducted in 4055 males aged 16-26 years with the primary efficacy objective of demonstrating reduction of the incidence of external genital lesions related to HPV 6, 11, 16, or 18. An observed efficacy of 65.5% was noted in the intention-to-treat population while an efficacy of 90.4% was noted in the per-protocol group against lesions related to HPV 6, 11, 16, or 18[25]. Studies have also been conducted to measure the immune response to the vaccine in boys. A non-inferiority immunogenicity study was performed to establish the efficacy of the quadrivalent HPV vaccine in adolescent boys and girls from age 10-15. The resulting immune response in boys was found to be similar to their female counterparts[26]. These studies ultimately led to FDA approval for use of HPV vaccine in males ages 9-26 in 2010. Safety data in males has been similar to that documented in the female cohort. The most common side effects associated with vaccination include headache, pain at injection site, itching, redness, swelling and bruising[25].

A study by Bogaards *et al*[27] in the Netherlands recently looked at the benefit of including boys 12 years of age in the HPV vaccination program. The authors found that in order to prevent one additional case of anal, penile or oropharyngeal cancer among men, 795 boys would need to be vaccinated[27]. Alternatively, if vaccine coverage among girls increased from 60% to 90%, the burden of HPV related cancer in men would be reduced by 66%. This data suggests that even if vaccination increased dramatically just for girls, it would not influence the burden of anal cancer that is found primarily in men having sex with men. Therefore vaccination of boys may provide additional benefit although the cost effectiveness of this strategy comes into question[27].

In the United States, the HPV vaccine is recommended for routine vaccination at age 11 or 12 for both boys and girls. "Catch up vaccination" is also recommended for females aged 13 through 26 and males aged 11 through 21 who have not been previously vaccinated, for men who have sex with men and men who are immune-compromised through age 26[28].

Despite these recommendations, vaccination rates remain low among adolescent boys. In 2013, HPV vaccination among adolescent boys was 34.6% and in men who have sex with men aged 18-26, vaccination was significantly lower[29]. In a study of 428 gay and bisexual men aged 18-26, Reiter *et al*[30] found that only 13% of the study population had received any doses of vaccine. Another study by Meites *et al*[31] evaluated data from the 2011 National HIV behavioral surveillance system of 3221 men who have sex with men aged 18-26 and found that only 4.9% reported receiving 1 or more HPV vaccine doses. Rates of HPV vaccination also vary widely by state and region in the United States. For men, the rate of vaccine initiation and completion was 8.5% and 2.2% in the Northeast, 6.7% and 1.6% in the West and 4.9% and 1.4% in the South. For women, the rate was 58.7% and 45.6% in the Northeast, 39.0% and 24.8% in the West and 30.4% and 17.7% in the South[32].

HPV vaccination in the immunocompromised: Given the high rates of HPV infection and HPV associated cancers in HIV positive and other immunocompromised populations, HPV vaccination should be considered in these groups[33]. Several different bacterial and viral vaccines are recommended for use in solid organ transplant patients, including pneumococcal, influenza, hepatitis A virus, hepatitis B virus, diphtheria, and tetanus vaccines. These patients have diminished, but often effective, immune responses, with no major consequences[33,34]. Given that HPV VLPs represent highly immunogenic proteins as seen by the degree of humoral response in immunocompetent women, the HPV vaccine causes adequate response in even immunocompromised individuals[33]. The benefit of vaccination preventing reactivation of HPV remains unknown.

Individuals with HIV are known to be at significant risk for persistent HPV infection and the sequelae associated with persistent infection, including neoplasia and malignancy[35]. Vaccine safety and immunogenicity in at-risk populations has been studied among men, women, and children with HIV[35-39]. A randomized clinical trial found the vaccine to be safe and immunogenic in 126 HIV-infected children aged 7-12 years. By 18 mo 94%-99% had antibody to HPV 6, 11 and 16 while 76% had antibody to HPV 18[37]. Weinberg *et al*[38] examined immunogenicity of 3 *vs* 4 doses of the quadrivalent vaccine in children aged 7-12 years with HIV. Following three doses the immune response to HPV 6, 11, and 16 were sufficient, however seropositivity remained lower for HPV 18. In the cohort receiving a fourth dose of vaccine, seropositivity of HPV 18 increased to levels equivalent to HPV 6, 11, and 16[38]. Another study of 109 HIV-infected males also found the vaccine to be immunogenic and well tolerated. Responses appeared to be higher for males on antiretroviral therapy as compared to those not receiving treatment[39]. In a study by Kahn *et al*[35], the quadrivalent HPV vaccine was shown to be safe and immunogenic in HIV positive women aged 16-23 who were previously HPV seronegative[35].

In the United States, vaccination is currently recommended by the Advisory Committee on Immunization Practices through age 26 years for immunocompromised persons who have not been vaccinated previously or who have not completed the 3-dose series[34].

HPV vaccination programs and cost effectiveness

In 2014, the World Health Organization (WHO) released updated recommendations for HPV vaccination in countries where preventing cervical cancer is a public health priority and where it is both feasible and financially sustainable to introduce the vaccine. The

WHO recommended that in these countries, girls aged 9-13 be the primary target group for vaccination, prior to becoming sexually active[40]. As of June 2015, 82 countries worldwide had introduced vaccination programs. Most of the vaccination programs are directed at pre-teen and teenage children, and some specifying vaccination for females only. There are multiple countries identified by the WHO statistics that have HPV vaccination programs (Table 2). These include 12 African countries, 2 Eastern Mediterranean countries, 31 European countries, 3 South-East Asian countries, and 15 Western Pacific countries. Additionally, 7 more countries have plans to introduce vaccination programs in the coming years[41].

The WHO recommends evaluating cost effectiveness of HPV vaccination prior to implementation in countries. Studies have suggested that the most important determinant of cost effectiveness of HPV vaccination is the vaccine price, cost effectiveness threshold utilized, and whether or not screening is assumed to be in place[42]. In settings with established cervical cancer screening programs, under certain assumptions, studies have shown that HPV vaccination can reduce incidence and mortality of cervical cancer and incidence of abnormal pap tests and precancerous lesions that typically require costly follow up[42-44]. These models assume that early vaccination will lead to starting screening at later ages, and at reduced frequency, ultimately saving money in the long term.

Unfortunately in low and middle-income countries these studies have been more limited due to many different issues these countries face. There has been conflicting data within the same countries in terms of evidence of cost effectiveness[42]. This may be due to varied models used and assumptions made. In a review evaluating cost effectiveness of HPV vaccination in low and middle-income countries, introduction of HPV vaccines was found to be cost effective in 22 studies for girls aged 12 and younger[42]. Almost all these studies assumed three-dose vaccine coverage of > 70%, life long protection and did not assess delivery and program costs. Pooled results across all these studies suggest that even in countries where screening may be limited or non-existent, vaccination may be even more cost effective as long as the price for the vaccine is low[42]. Reasons for these conclusions include the competitive prices given for vaccines relative to the income level of the country, donor funding availability and high cervical cancer burden found in these countries with limited treatment options. Savings resulting from improved screening and HPV vaccination ultimately will depend on the actual costs in a given country.

HPV vaccine acceptability

Although the FDA has approved the HPV vaccine in the United States since 2006, vaccination rates have varied across countries and populations within countries[45]. Both developing and developed countries such as the United States (34% full coverage) and France (28.5% full coverage) have shown poor complete uptake rates[45]. Reasons for this include lack of knowledge and education in both adolescents and parents, cost associated with vaccine, lack of access to primary care or providers that offer vaccination and lack of provider recommendation[46-48] (Table 3).

Despite the relatively low vaccine coverage in the United States, a study did show that the prevalence of HPV subtypes 6, 11, 16, and 18 in cervicovaginal specimens in females aged 14-19 decreased from 11.5% in the pre-vaccine era to 5.1% in the vaccine era. Whereas in other age groups, the prevalence did not differ significantly between the two time periods[49]. In the United States, HPV awareness and knowledge are increasing compared to previous national surveys of HPV knowledge, with 68% of the adult population reporting knowledge of both HPV and the HPV vaccine[48]. However, this number is not consistent across populations and states. Globally, similar problems exist[46-48,50]. In the Uyghur population of China, younger women and those with a lower educational level were less likely to understand the correlation between HPV and cervical cancer[47].

Multiple studies have addressed the barriers to HPV vaccination especially as it relates to education. Barriers identified include lack of access to schooling, as well as cultural and linguistic differences[51]. Many of the adult population site obstacles to vaccination due to limited education, resulting in poor parental knowledge, holding jobs with difficult work hours, and childcare difficulties[52]. Many studies have focused on educating both patients and parents to increase awareness and vaccine acceptance; however the best method of delivery of these materials remains to be seen. Tools used in the past include educational sessions and focus groups, the media, videos, school-wide vaccination programs, and flyers[50-57] (Table 3).

School-based education has been attempted as a method to optimize uptake of the HPV vaccine. In a Korean study, fifth-grade girls and boys underwent a 2-h education session regarding the connection between HPV and cancer, as well as the effectiveness of the HPV vaccine. Awareness that "HPV vaccine can prevent cervical cancer" was significantly related to intention to obtain the HPV vaccine among both boys and girls[50].

A lower HPV vaccination rate has been seen among minority populations in the United States. Studies have shown poor vaccination rates among Black, Latina, and Asian girls in comparison to Caucasian girls[53]. Efforts have been focused on addressing individual populations to help increase acceptability. An educational video addressing HPV and vaccination was utilized as an intervention to a primarily underserved, lower income Black and Hispanic population of women. Acceptance of individual vaccination, mandatory HPV vaccination and support for school vaccination all increased significantly after the video based on survey responses[54].

In a study performed in Canada, parents were

Table 2 Worldwide vaccination protocols

	Country	Vaccine in schedule (as of December 31, 2014)	Year of introduction in entire country	Target population	Schedule
Africa	Botswana	No	2015	Girls 9-13 yr	3 doses
	Lesotho	Yes	2012	9-14 yr	3 doses
	Malawi	No	2015	Girls 9-13 yr	3 doses
	Rwanda	Yes	2011		3 doses
	Seychelles	Yes	2014	Girls 10-12 yr	
	South Africa	Yes	2014	9 yr	2 doses
Americas	Argentina	Yes	2011	11 yr	3 doses
	Barbados	Yes	2014	11 yr	2 doses
	Brazil	Yes	2014	9-14 yr	2 doses
	Canada	Yes	2009		3 doses
	Colombia	Yes	2012	9-17 yr	3 doses
	Ecuador	Yes	2014	9 yr	2 doses
	Guyana	Yes	Not available	Special groups	3 doses
	Mexico	Yes	2012	10 yr	2 doses
	Panama	Yes	2008	10 yr	3 doses
	Paraguay	Yes	2013	10 yr	3 doses
	Peru	Yes	2011	10 yr	3 doses
	Suriname	Yes	2013	9 yr	
	Trinidad and Tobago	Yes	2013	Females 11-45 yr, males 11-26 yr	3 doses
	United States	Yes	2006	11-26 females, 11-21 males (26 if high risk)	3 doses
	Uruguay	Yes	2013	12 yr	3 doses
Eastern Mediterranean	Bahrain	No			
	Libya	Yes	2013	15 yr	3 doses
Europe	Andorra	Yes	2014	12 yr	
	Austria	Yes	2008	9 yr	3 doses
	Belgium	Yes	2011	12 yr (13-14 in Wallonia)	3 doses
	Czech Republic (the)	Yes	2012	13 yr	
	Denmark	Yes	2007	12 yr	3 doses
	Finland	Yes	2013	11-12 yr	
	France	Yes	2006	Girls 11-14 yr	3 doses
	Germany	Yes	2007	Girls 12-17 yr	3 doses
	Greece	Yes	2009	11-18 yr	3 doses
	Hungary	Yes	2014	12 yr	
	Iceland	Yes	2011	12 yr	3 doses
	Ireland	Yes	2010	Girls 12-13 yr	3 doses
	Israel	Yes	2010	13 yr (or women 9-45 yr)	3 doses
	Italy	Yes	2009	Girls 12 yr	3 doses
	Latvia	Yes	2010	12 yr	3 doses
	Luxembourg	Yes	2008	12-18 yr	
	Malta	Yes	2013	12 yr	3 doses
	Monaco	Yes	2006	14 yr	3 doses
	Netherlands (the)	Yes	2010	12 yr	2 doses
	Norway	Yes	2009	Girls 12 yr	3 doses
	Portugal	Yes	2008	10-13 yr	3 doses
	San Marino	Yes	2008	11 yr	
	Slovenia	Yes	2009	11-12 yr	2 doses
	Spain	Yes	2007	12 yr	3 doses
	Sweden	Yes	2010	Girls 10-12 yr	3 doses
	Switzerland	Yes	2006	Girls 11-14 yr	3 doses
	The former Yugoslav Republic of Macedonia	Yes	2009	12 yr	3 doses
	United Kingdom	Yes	2008	12-13 yr	2 doses
	Uzbekistan	No	2015		
South-East Asia	Bhutan	Yes	2009	Girls 12 yr	3 doses
Western Pacific	Australia	Yes	2007	10-15 yr	
	Brunei Darussalam	Yes	2012	13 yr	3 doses
	Cook Islands	Yes	2011	9 yr	
	Fiji	Yes	2013	13 yr	
	Japan	Yes	2011	13 yr	3 doses
	Malaysia	Yes	2010	Girls 13 yr	3 doses
	Marshall Islands (the)	Yes	2009	11-12 yr	
	Micronesia (Federated States of)	Yes	2010	9 yr	3 doses
	New Zealand	Yes	2009	12 yr (and other eligible individuals)	3 doses
	Palau	Yes	2008	9-26 yr	3 doses
	Philippines (the)				2 doses
	Singapore	Yes	2010	Girls 9-26 yr	3 doses

Table 3 Possible interventions to increase human papillomavirus vaccine uptake

Ref.	Year	Country	Objectives	*n*	Outcome	Target population	Educational tools
Chapman *et al*[54]	2010	United States	Evaluation of a video-based educational tool to increase HPV vaccine acceptability	256	Vaccine acceptability increased following intervention	Women aged 18-60	8 min video
Kennedy *et al*[55]	2011	United States	Improvement of HPV vaccine educational materials and determination of efficacy	411	Increase in likelihood of vaccination of children and favorable view of HPV vaccine	Parents of girls 11-18 yr of age	Educational flyer
Kobetz *et al*[51]	2011	Haiti	Assessment of women's knowledge and beliefs regarding cervical cancer and HPV		Need for culturally and linguistically appropriate educational initiatives	Haitian immigrant women in Miami, FL	Focus groups
Kester *et al*[56]	2014	United States	Evaluation of the effects of a brief education session on HPV awareness	131	Higher vaccination intent among intervention group	18-26 yr old females and males	5-10 min education session
Kim[50]	2015	South Korea	Assessment of knowledge of HPV relation to cancer in children	117	HPV education at elementary school would be helpful	Fifth-grade girls and boys	2 h education session
Nodulman *et al*[57]	2015	United States	Evaluation of feasibility of increased immunization rates through middle school vaccination programs	117	Low acceptance of middle school vaccination by adolescents, parents and stakeholders	Middle school stakeholders, nurses, parents, adolescents, administrators	Middle school vaccination program

HPV: Human papillomavirus.

Table 4 Evaluation of barriers to human papillomavirus vaccination

Ref.	Year	Country	Target population	Objectives	*n*	Identified barriers to vaccination
Mortensen[46]	2010	Denmark	Women aged 16-26	Evaluation of reasons for acceptance or rejection of HPV vaccine following general vaccine availability	794	Cost, lack of information about the benefits of vaccination, and lack of knowledge about HPV
Ogilvie *et al*[58]	2010	Canada	Parents with daughters in 6th grade	Determination of parental factors associated with receipt of the HPV vaccine in a publicly funded school-based HPV vaccine program	2025	Lack of knowledge regarding the HPV vaccine
Kobetz *et al*[51]	2011	United States	Haitian immigrant women in Miami, FL	Assessment of women's knowledge and beliefs regarding cervical cancer and HPV		Lack of education
Jeudin *et al*[53]	2014	United States	Black and Latina populations	Identification of barriers to uptake of HPV vaccination among low-income and minority girls		Lack of access to primary care, lack of provider recommendation, lack of parental knowledge
Kim[50]	2015	South Korea	Fifth-grade girls and boys	Assessment of children's knowledge regarding HPV and association with cancer	117	Lack of HPV knowledge, lack of HPV education in schools
Abudukadeer *et al*[47]	2015	China	Women in Xinjiang province	Assessment of knowledge and perception of cervical cancer	5000	Lack of knowledge about cervical cancer
Blake *et al*[48]	2015	United States	National Cancer Institute's 2013 Health Information National Trends Survey Data	Assessment of population knowledge regarding HPV and the HPV vaccine as well as socioeconomic disparities	3185	Lack of HPV awareness and knowledge
Nodulman *et al*[57]	2015	United States	Middle school stakeholders, nurses, parents, adolescents, administrators	Increase of immunization rates through middle school vaccination programs	117	Lack of knowledge about HPV vaccine

HPV: Human papillomavirus.

interviewed to assess which factors were the most important barriers to vaccinating their children. The study was performed in a publicly funded, school-based HPV vaccine program, to remove the barriers of access and cost. Despite this, the main reasons for not vaccinating female children were concerns about vaccine

safety, preference to wait until the daughter is older, and not having enough information to make an informed decision[58]. Based on this study it is apparent that even when financial and health care barriers are removed, parental acceptance of vaccination remains critical in improving vaccine uptake (Table 4).

It has been shown that countries using school-based vaccination programs have the most success in uptake. Countries such as Australia, United Kingdom, and Portugal have achieved coverage rates as high as 80%[52]. Denmark has reached one of the highest vaccination rates (> 80%) through aggressive administration by general practitioners[52]. In Rwanda, government-mandated HPV vaccine coverage achieved over 90% coverage among teenage girls[59]. Programs that have achieved mass vaccination coverage rates have been able to show reduction in HPV viral prevalence in the form of high grade precancerous lesions and overall disease burden.

Vaccination strategies: Overall strategies to achieve mass vaccination continue to point towards a comprehensive approach. Continuing to raise awareness about cervical cancer and its relationship to HPV while addressing misconceptions and safety concerns to a wide range of audiences through education and health communication programs remains essential. All strategies should to be country-specific and take into account not only women, but communities, health professionals and delivery methods that provide the highest likelihood of exposure to the general public. In many developing countries, older children and adolescents are rarely routinely vaccinated or routinely evaluated by primary health care providers. New systems will need to be created including a focus on school-based immunization programs, and creating partnership programs focusing on adolescent health and sexual reproductive health programs.

CONCLUSION

Development of HPV vaccines has created opportunities to reduce cervical cancer rates and morbidity associated with other HPV related diseases. These vaccines have been found helpful in both countries with effective screening programs and those without. Financing for HPV vaccination programs will require involvement of global partners in both the private and public sector. Ongoing research regarding long term safety and efficacy of HPV vaccines will need to be evaluated in a variety of populations including those areas with high HIV prevalence. More information is needed regarding the duration of vaccine protection, long-term efficacy in males, potential need for boosters, and efficacy of two dose regimens in older girls that may reduce the overall costs of the vaccine. If uptake in vaccination increases worldwide, it may lead to increased possibilities of developing prevention and screening programs due to a subsequent decline in disease incidence.

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