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American Society of Clinical Oncology Statement: Human Papillomavirus Vaccination for Cancer Prevention

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ABSTRACT

American Society of Clinical Oncology (ASCO), the leading medical professional oncology society, is committed to lessening the burden of cancer and as such will promote underused interventions that have the potential to save millions of lives through cancer prevention. As the main providers of cancer care worldwide, our patients, their families, and our communities look to us for guidance regarding all things cancer related, including cancer prevention. Through this statement and accompanying recommendations, ASCO hopes to increase awareness of the tremendous global impact of human papillomavirus (HPV)–caused cancers, refocus the discussion of HPV vaccination on its likely ability to prevent millions of cancer deaths, and increase HPV vaccination uptake via greater involvement of oncology professionals in ensuring accurate public discourse about HPV vaccination and calling for the implementation of concrete strategies to address barriers to vaccine access and acceptance.

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INTRODUCTION

American Society of Clinical Oncology (ASCO) is the leading medical professional oncology society committed to conquering cancer through research, education, prevention, and delivery of high-quality patient care. As such, ASCO is determined to pursue and support discovery of interventions that lessen the burden of cancer on our patients, their families, and our communities. Moreover, we are obligated to promote underused interventions that have the potential to save millions of lives through cancer prevention. Vaccinations against cancer-causing infections are such an intervention. Recent data estimate that 10% of yearly cancers worldwide (or > 1 million cases per year) are caused by viral infections.[1] This number translates into more than a half million lives lost each year to virus-caused malignancies. The bulk of these cancers and resultant deaths are attributable to a relatively small number of viruses: human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus, and Epstein-Barr virus, which cause, respectively, 600,000, 380,000, 220,000, and 110,000 cancer cases per year.[2]

The concept of eradicating viral-associated malignancy via vaccination is not new, nor is the ability to nearly eradicate a disease with vaccination (eg, polio). Although research continues regarding development of vaccinations against infection with hepatitis C virus, Epstein-Barr virus, and other viruses, vaccinations against HBV and some strains of HPV already exist. For example, HBV vaccines have been available for many years. Some countries (eg, Taiwan and Korea) with endemic HBV infection and resultant high rates of hepatocellular carcinoma (HCC) implemented universal infant HBV vaccination policies in the 1980s and have experienced ongoing evidence of dramatic reductions in HBV infection, resultant hepatitis, and, more importantly, reductions in HCC incidence and mortality.[3]

Bivalent, quadrivalent, and, more recently, nonavalent (nine-valent) vaccines against HPV genotypes (targeting those most commonly causing cancer globally) are approved in the United States and other countries for primary prevention of HPV infections because of their strong safety record and their ability to prevent new cancer-causing HPV genotype-specific infections and resultant diseases, such as grade 2 and 3 cervical intraepithelial neoplasias (CIN), vaginal, vulvar, and anal intraepithelial neoplasias (as precursor lesions to cancer).[4] Despite the almost certainty that cancers caused by oncogenic HPV genotypes will be dramatically reduced, the use of HPV vaccination in the United States is low (36% and

14% of girls and boys, respectively, age 11 to 13 years have received all three doses), and use worldwide is variable.[5]

In addition to the numerous reports and recommendations that have been issued by national and state-level bodies and organizations, a number of professional medical organizations have voiced concern about the lack of uptake of HPV vaccination and have issued statements supporting the implementation of this cancer-reducing strategy (Table 1). As an organization committed to lessening the burden of cancer in the United States and worldwide, ASCO has developed this statement to provide the rationale behind, and a roadmap for, increasing HPV vaccination uptake as a means of preventing HPV-related cancers and saving the lives of millions.

HPV-RELATED CANCER

Cervical cancer is the most prevalent HPV-related cancer and the fourth most common cancer in women.[6] It is also the second most common cancer worldwide in women between the ages of 15 and 44 years.[7,8] In 2012, there were 528,000 new cases of and more than 266,000 deaths resulting from cervical cancer globally, with the vast majority of these deaths occurring in less developed regions.[9] HPV is the cause of nearly all cervical cancer cases, and HPV genotypes 16 and 18 are responsible for 70% of cervical cancers.[6,10] In the United States, HPV is responsible for 60% of oropharyngeal cancers, 90% of which are caused by HPV 16.[11] HPV is also the cause of 91% of anal cancers, 75% of vaginal cancers, 69% of vulvar cancers, and 63% of penile cancers, again with HPV 16 as the predominant oncogenic genotype (Table 2).[12] Most importantly, HPV-related cancers affect both men and women. In fact, oropharyngeal cancers caused by HPV are three to five times more common in men,[11] which emphasizes the importance of HPV infection and eradication as non–sex-specific issues.

HPV-related cancers seem to be disproportionately distributed among those of lower income and lower educational attainment and various racial/ethnic groups. Low educational attainment and low income have been found to be associated with higher risks of penile, vaginal, and cervical cancers.[14] According to the SEER database, the incidence rate of cervical cancer is higher in Hispanic and African American women than that in non-Hispanic white women in the United States.[15] Contributing factors for this disparity include low screening and treatment rates and behavioral risk factors, such as relatively early age at first sexual activity.[16]

Efficacy and Safety of HPV Vaccines

HPV vaccines have been available since 2006. Gardasil (Merck, Kenilworth, NJ) and Cervarix (GlaxoSmithKline, Brentford, United Kingdom) are currently approved in approximately 100 countries, offering complete protection for HPV-naïve girls and young women against the known oncogenic HPV genotypes 16 and 18. Both vaccines have a known duration of protection of at least 5 years, with ongoing study of the full duration of their effect.[17] In December 2014, the US Food and Drug Administration approved Gardasil-9, which adds protection against five additional oncogenic HPV types (ie, 31, 33, 45, 52, and 58) when compared

Table 1. HPV Vaccine Recommendations of National Medical Organizations

Organization	Action	Link
American Academy of Family Physicians, American Academy of Pediatrics, American College of Obstetricians and Gynecologists, American College of Physicians, Centers for Disease Control and Prevention, and Immunization Action Coalition	Collaborative letter urging physicians to strongly recommend the HPV vaccine	http://www.aafp.org/dam/AAFP/documents/patient_care/immunizations/hpv-recommendation-letter.pdf
American Cancer Society	Recommendations for HPV vaccine use to prevent cervical cancer and precancers	http://www.cancer.org/cancer/cancercauses/othercarcinogens/infectiousagents/hpv/acs-recommendations-for-hpv-vaccine-use
American College of Obstetrics and Gynecology	Committee opinion on HPV vaccination	http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Adolescent-Health-Care/Human-Papillomavirus-Vaccination
American Dental Association	Statement on HPV and squamous cell cancers of the oropharynx	http://www.ada.org/en/about-the-ada/ada-positions-policies-and-statements/statement-on-human-papillomavirus-and-squamous-cel
American Head and Neck Society	Position statement on HPV vaccination for prevention of HPV-related oropharyngeal cancer	https://www.ahns.info/wp-content/uploads/2015/10/HPV-Position-Statement-10-9-2015.pdf?8a5c02
American Nurses Association	HPV background paper and call for legislative action	http://www.nursingworld.org/MainMenuCategories/Policy-Advocacy/ExpiredContent-GOVA/IssuesResources/HPV/HPV.pdf
American Pharmacists Association	Role of pharmacists in improving HPV vaccination rates among adolescents	http://www.pharmacist.com/node/29316
Association of Immunization Managers	HPV call to action	http://www.immunizationmanagers.org/?page=CalltoAction&hhSearchTerms=%22HPV%22&#rescol_1056122
Society for Adolescent Medicine	Position statement on HPV vaccination	http://www.adolescenthealth.org/SAHM_Main/media/Advocacy/Positions/Oct-06-HPV-position.pdf
Society of Gynecologic Oncology	Position statement: HPV vaccination of girls and boys	https://www.sgo.org/newsroom/position-statements-2/hpv-vaccination-of-girls-and-boys-2/

Abbreviation: HPV, human papillomavirus.

Table 2. HPV-Related Cancers[11-13]

Cancers Caused by HPV in the United States
Approximately 99.7% of cervical cancers
60% of oropharyngeal cancers
91% of anal cancers
75% of vaginal cancers
69% of vulvar cancers
63% of penile cancers

Abbreviation: HPV, human papillomavirus.

with the original bivalent and quadrivalent vaccines. The new Gardasil-9 has the potential to prevent approximately 90% of cervical, vulvar, vaginal, and anal cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58. Efficacy and safety studies of all three HPV vaccines have had remarkably similar results.

A long-term follow-up observation of the safety and efficacy of Gardasil in adult women who were HPV negative before receiving the vaccine and received all three doses of the vaccine demonstrated there were no cases of HPV 6-, 11-, 16-, or 18-related cervical intraepithelial lesions or external genital lesions during the extended follow-up, with persistent immunogenicity and absence of any serious adverse events (median follow-up, 6.26 years).[18] Because of the long latency and the prolonged preinvasive phase after infection with HPV, many years of follow-up are needed for the ongoing trials to demonstrate a significant reduction in HPV-related cancers. Therefore, intermediate outcomes, such as decrease in precancerous lesions (ie, CIN), are considered acceptable surrogate end points for reduced incidence of cervical cancer.[19] According to the report by the Centers for Disease Control and Prevention (CDC) in 2012, an estimated 53,000 additional cases of cervical cancer could be prevented by increasing three-dose HPV vaccination coverage to 80%.[20] Both Gardasil and Cervarix vaccines reported excellent short- and long-term safety results in clinical trials. The most common adverse effects were mild and included injection site pain (approximately nine in 10 people) and swelling (approximately one in three), fever (approximately one in eight), headache, and fatigue (approximately one in two).[21] These symptoms were transient and resolved spontaneously. The incidence of serious adverse effects was low and was similar to those who received placebo (aluminum-containing placebo or hepatitis A vaccine).[22] The Gardasil-9 vaccine was also shown to have high efficacy and safety results in clinical trials. Rates of cervical, vulvar, and vaginal disease related to HPV type 31, 33, 45, 52, or 58 were lower in participants who received all three doses and who were HPV negative at the time of the first injection, compared with those who received the quadrivalent vaccine.[23] Adverse effects included mild or moderate pain, swelling, redness, or itching at the injection site; headache; fever; nausea; dizziness; and fatigue.

Current Vaccination Recommendations

Because of the excellent efficacy and safety profiles of the approved HPV vaccines, the CDC recommends that all boys and girls age 11 or 12 years get vaccinated. For adults, vaccines are recommended for men through age 21 years and women through age 26 years. Furthermore, the CDC recommends vaccination for gay and bisexual men through age 26 years and for men and women with compromised immune systems through age 26 years if they did not get fully vaccinated at a younger age. The Advisory Committee on Immunization Practices has nearly identical recommendations.[24,25]

All of the three currently available vaccines are recommended for girls and young women, whereas only the quadrivalent (Gardasil) and nonavalent (Gardasil-9) vaccines are recommended for boys and young men. Currently, the US Food and Drug Administration recommends three doses, with the second and third doses administered 1 to 2 months and 6 months after the first dose, respectively. The HPV vaccines are contraindicated in those who are severely allergic to any component of the vaccine and pregnant women.[21] In December 2014, the WHO released "Comprehensive Cervical Cancer Control: A Guide to Essential Practice," calling for the vaccination of all girls age 9 to 13 years with the two-dose vaccine schedule with an interval of 6 months, noting the change will make it easier to administer and reduce costs. The three-dose schedule should continue to be recommended for those who are immunocompromised and for young women age 15 years or older.[26]

HBV: A COROLLARY TO HPV VACCINATION

Before HPV was recognized as a potentially cancer-causing virus, HBV had become largely accepted as one of the most common cancer-inducing viruses in the world. Because HBV can be easily transmitted via blood or body fluids or perinatally and is 50 to 100 times more infectious than HIV, its infectious potential has become widely recognized as an endemic matter of importance.[27] WHO states that 2 billion people have been infected by HBV.[28] Approximately 240 million people have chronic HBV infection, contributing to an estimated 786,000 deaths worldwide each year.[27,29] Twenty-five percent to 40% of all individuals with chronic HBV will develop serious long-term sequelae, such as liver cirrhosis and HCC.[30] As oncologists, we are keenly aware that only a few select patients with HCC have curative options, and patients with unresectable HCC have highly limited treatment options and poor overall survival.[31] Hence, the global economic impact for those affected by HBV is significant.

Since 1982, more than 1 billion doses of HBV vaccine have been administered worldwide. At an initial cost of $100 for three doses, the price was felt to be too costly for the general public.[32] However, with increased advocacy, expired patents, and vaccine development outside the United States, the price was eventually reduced to $1.00 per dose within a decade. With the realization that low- and middle-income countries were in dire need of the vaccine, the price was then further reduced to $.20 per dose. In 1992, the WHO advocated for the HBV vaccine to be considered part of the standard immunization panel in all countries. In 2000, with the support of many, the Global Alliance for Vaccine and Immunization (GAVI Alliance) was created. The primary focus of the GAVI Alliance was on subsidizing new vaccines for low- and lower-middle–income countries to reduce the lag time between the development and the introduction of new childhood vaccines. The GAVI Alliance (now called Gavi, the Vaccine Alliance) estimates that 3.7 million deaths resulting from HBV infection have been prevented by vaccine programs created during the years 2000 to 2011.[33]

In the United States, strategic support by the CDC since 1982 has resulted in: all newborns being vaccinated, screening of all pregnant women for hepatitis B surface antigen and screening of all newborns born to hepatitis B surface antigen–positive women, vaccination of all children and adolescents, and 4) vaccination of all at-risk individuals. Before the CDC strategic implementation, it was estimated 200,000 to 300,000 individuals were infected annually with HBV, of whom 7% to 10% were children.[34] After two decades of implementation, it was estimated 40 million infants and children and 30 million adults had received the HBV vaccine.[35] As a result, the number of persons infected declined to an estimated 79,000 in 2001. In short, since 1990, new HBV infections among children and adolescents have been reduced by more than 95% and by 75% in all other age groups.[36]

Globally, as of 2011, 180 countries now include the HBV vaccine in their routine vaccine schedules, and coverage is approaching 80%. In many countries, where 10% to 15% of children used to become chronically infected with HBV, vaccination has reduced the rate of chronic infection to less than 1% among immunized children.[6] The most recent progress in reducing HBV-related cancers through vaccination programs is clearly demonstrated in Asia, where the prevalence of chronic HBV infection is greatest. Asians and Pacific Islanders comprise more than 50% of Americans living with chronic HBV; one in 12 individuals are not aware they are positive for HBV.[8] In the United States alone, Asians and Pacific Islanders reported a dramatic decline of acute, symptomatic HBV from 3.7 cases per population of 100,000 in the year 2000 to 0.7 cases per population of 100,000 in 2009.[37] Taiwan, for example, is largely seen as one of the most successful national vaccination programs, where more than 90% of the general population was infected with HBV before implementation of the program. Since the launch of the program in 1984, the annual incidence of HCC has been reduced significantly in individuals 6 to 19 years of age.[38] Because of cost, widespread HBV vaccination in China did not start until the early 2000s. However, it is estimated that with the assistance of Gavi (from 2003 to 2009), approximately 3.8 million chronic HBV infections and 680,000 deaths were prevented in China.[39]

The global health care initiative to reduce the burden of HBV via vaccine intervention and the resultant reduction in the sequelae of HBV (eg, cirrhosis and cancer) comprise an exemplary health model that supports more widespread HPV vaccination. In addition to a proof of principle, HBV infection and vaccination provide a potential roadmap for wider acceptance, application, and corroboration of the likely impact of widespread HPV vaccination. In both cases, vaccination is best administered early in age (infancy for HBV and preadolescence for HPV) to have the greatest effect toward reducing the risk of cancer. Moreover, widespread acceptance benefits from involvement of key opinion leaders in medicine, pharmaceutical companies, patient advocates, politicians, and philanthropists, as created in Gavi.

HPV VACCINATION IMPLEMENTATION AND EARLY RESULTS

In 2007, Australia became one of the first countries to provide a nationally financed program of quadrivalent HPV vaccine for girls and young women between 12 and 18 years of age (Table 3). In 2010, the HPV vaccination rate was reported to be 83% for the first dose and 73% for the third dose in girls age 12 to 13 years.[48] The success of the program led to a large decline in genital warts, from 11.3% in 2007 to 3.1% in 2011 for women age 21 to 30 years.[48] A systematic review and meta-analysis of the population-level impact after HPV programs showed that in countries with HPV vaccination coverage of at least 50% for girls and young women, there was a significant decrease (68%) in HPV 16 and 18 infections before and after the vaccinations periods, including a 61% decrease in anal and genital warts in girls and young women 13 to 19 years of age.[49] Through support from Gavi, the Pan American Health Organization Revolving Fund, and Merck, multiple low- and middle-income countries worldwide have received reduced the cost of vaccination (eg, $< $10 per dose) or established free vaccination through regional or nationwide administration programs. In Rwanda, free vaccines were provided for 3 years to 93,888 elementary school–age girls, with 90% of all Rwandan girls receiving the first dose, followed by 94% receiving the second and 93% the third.[50] The success of the Rwandan program is attributed to school-based vaccination as well as active community involvement, factors that have been shown to be positively associated with HPV vaccination uptake in other low-income regions of the world. A 2012 study reported the results of three types of HPV vaccination programs through the Gardasil Access Program in seven of the lowest-income countries.[51] The success of these programs varied by model: the mixed model (health facility and school based; 96.6%), the school-based model (88.6%), and the health facility–based model (79.9%). When examining large-scale vaccination programs, the sharpest decline in HPV-related outcomes in both male and female participants was noted in countries with school-based vaccine delivery (eg, the United Kingdom, Australia, and New Zealand).

Similar to the results seen elsewhere, HPV vaccination rates in the United States and Canada vary greatly and are highest in areas or states with specific vaccination plans and programs including school-based vaccination.[52] In Rhode Island, for example, grade 7 boys and girls are required to receive bundled Tdap (tetanus, diphtheria, and pertussis), meningococcal virus, and HPV vaccines. Early success was recently reported, with a first-dose administration rate of 72.5%.[53] These findings have important policy and strategic implications for successful HPV vaccination programs.

BARRIERS TO HPV VACCINATION

Despite the CDC recommendation that all boys and girls receive the HPV vaccine at age 11 to 12 years, data from the National Immunization Survey in 2011–Teen revealed low compliance with recommended vaccination regimens. Approximately 36% of girls have received all three doses of the HPV vaccine, and only 14% of boys have completed the series.[5] Rates of completion of the HPV vaccine series are even lower in high-risk populations (eg, Hispanics, blacks, and the poor), further increasing the health care disparity prevalent in patients who are most vulnerable to developing cervical cancer.[54] With the current low uptake rate of 34.8%, it is unlikely the objective set by Healthy People 2020 of 80% vaccine completion for girls age 13 to 15 years will be achieved by 2020.[55,56]

Table 3. International HPV Vaccination Programs[40-47]

Country	Year Implemented	Delivery Model	Policy
Australia	2007	School based	Eligible boys and girls age 12 to 13 years can receive vaccination free of charge through National HPV Vaccination Program
Belgium	2007	Health facility based	Opportunistic vaccination, partially financed (75%) by national health system
Brazil	2014	Health facility based	Offered to girls age 9 to 13 years
Canada	2007	School based	Free for girls age 9 to 15 years; currently offered to boys in two provinces (Prince Edward Island and Alberta)
France	2007	Health facility based	Voluntary vaccination of girls age 14 years, with catch-up program for girls and young women age 15 to 23 years; 65% of cost is financed by National Health Authority
Germany	2007	Health facility based	Free vaccination is available for girls age 12 to 17 years and for young women outside of this age group who are not yet sexually active
Greece	2008	Health facility based	Mandatory for all girls entering seventh grade; vaccination is free and financed through National Health System
Israel	2012	Mixed model	Girls in eighth grade receive vaccination free through schools only; girls in ninth grade receive vaccination free at Ministry of Health office locations only
Italy	2007	Mixed model	Universal vaccination provided free of charge for 12-year-old girls
Kenya	Pilot program began 2012	School based	Targets primary school girls age 9 to 14 years
Luxemborg	2008	Health facility based	Free vaccination is offered for 12-year-old girls and female adolescents age 13 to 17 years
Macedonia	2010	School based	National vaccination program targets 12-year-old girls; vaccination is free and financed through National Health System
Mexico	2008	Mixed model	Initial program delivered vaccine to girls age 12 to 16 years Program expanded nationwide in 2011 to provide school-based vaccination to all girls age 9 years
New Zealand	2008	Mixed model	Girls and young women age 9 years to their 20th birthday can receive Gardasil free under Ministry of Health HPV Immunization Program People; with diagnosed HIV, those younger than age 26 years can access free Gardasil vaccination
Panama	2008	Mixed model	Targets girls age 10 years through both clinics and schools
The Netherlands	2009	Health facility based	Free vaccination of 12-year-old girls
United Kingdom	2007	School based	All girls age 12 to 13 years are offered free vaccination as part of National Health Service childhood vaccination program

NOTE. Table is inclusive of publically available information and may not be exhaustive in its detail of all international programs.
Abbreviation: HPV, human papillomavirus.

Although barriers to HPV vaccination are multifactorial, and few advances have been seen since 2006, the success of vaccination programs seems highly dependent on the support and recommendations of public health officials and health care professionals. When parents and health care providers are asked about the low HPV vaccination rates, the following barriers are identified[57-61]:

- Limited understanding of HPV and HPV-related diseases, especially in men
- Being unaware of or forgetting about the need for additional doses
- Safety concerns about the vaccine
- Discomfort talking about sexual behavior
- Lack of time for discussions about the vaccine among clinicians
- Lack of a clear recommendation from a health care provider
- Parental belief that son or daughter is too young for the vaccine and/or not sexually active
- Lack of adequate reimbursement and concerns about cost of the vaccination to the patient
- Need for systems to remind clinicians to offer the vaccine to age-appropriate patients at the time of other routine vaccinations

The narrative regarding the HPV vaccine has been different from those for most adolescent vaccines. Rather than focusing on the life-threatening illness prevented (eg, meningococcal meningitis), the focus has been on the behavior associated with infection (ie, sexual activity). This has led to misplaced parental attitudes toward and understanding of the vaccine.[57,62] Studies have shown that parents do not understand the importance of the HPV vaccine or its impact on cancer prevention.[57,63] The lack of a clear recommendation from a health care provider is often cited as one of the reasons for not getting the HPV vaccine.[58,64]

Studies show once educated about the cancer-preventive properties of HPV vaccination, parents and practitioners are more likely to support HPV vaccination[57,63,64]; however, missed opportunities result from assumptions about the timing of vaccination relative to sexual activity.[63] HPV vaccination for boys and girls at an early age (11 to 12 years) rather than later ($\geq$ 18 years) is recommended for multiple reasons: the HPV vaccine is most effective when administered before a person becomes sexually active and before HPV exposure; HPV vaccination during early adolescence is associated with greater immunoreactivity and HPV antibody titer levels as compared with young adulthood[65]; and

early administration allows the HPV vaccine to be administered with other vaccines (or bundled) at age 11 years, leading to better vaccination uptake rates.[66] Providing patient-focused educational materials and training to midlevel professionals as well as practitioners will help address these barriers.[63,67]

Low- and Middle-Income Countries

In low- and middle-income countries, a primary barrier to HPV vaccination is cost. Although both Merck and GlaxoSmithKline have been able reduce prices to the world's poorest countries to less than $5 per dose ($4.50 for Merck and $4.60 for GlaxoSmithKline) through negotiation with Gavi, in the most economically disadvantaged countries (those with a gross domestic product of US $1,580 per capita), the per-dose cost may need to be as low as $1 to $2 to be cost effective and affordable.[65,68,69] To receive subsidized HPV vaccines from Gavi, a country must demonstrate prior experience with disseminating multidose vaccines to half of the target population, or countries can apply for support to conduct small demonstration projects.[70] In 2015, 49 countries were eligible for Gavi support on the basis of a gross national income per capita less than or equal to US $1,580. In the Americas, Haiti was the only country eligible for this support.[71] Although Gavi subsidies will help many countries obtain the HPV vaccine at a substantial cost reduction, countries will still need to budget for the delivery of the vaccine.

Another resource available to reduce the cost of the HPV vaccine is the Pan American Health Organization Revolving Fund for vaccine procurement, which has been in existence for more than 30 years. This fund helps 41 countries and territories pool their resources to procure the bivalent HPV vaccine, syringes, and related supplies for their populations at the lowest price of $8.50 per dose. The success of this program in the Americas has led to discussions about the expansion of the program to regions of Africa and the Eastern Mediterranean.[72] A challenge identified by Agost and Goldie[68] is that in "environments with a strong distrust of government, vaccination programs aimed at young women may be misunderstood as an attempt to control fertility".[68(p1908)]

In Latin America, the incidence of cervical cancer remains one of the highest in the world, and prevalence of HPV has been found to be twice as high as the average worldwide prevalence.[73] Barriers include a lack of health care infrastructure, cost effectiveness of vaccination compared with other needs competing for resources, and cultural acceptability.[10,65,74]

United States

Cost also remains one of the largest barriers to HPV vaccine administration in the United States, where all three doses of the Merck vaccine cost approximately $390, or $130 per dose.[74] However, expenditures for the provider include not only the cost to purchase the vaccine upfront, but also the time and staff needed to administer the drug. These costs, coupled with inadequate insurance reimbursement, make the HPV vaccine difficult to provide in primary care offices.[63] A national survey of primary care providers found that practitioners are dissatisfied with insurance payments regardless of payer type.[75] The Affordable Care Act (ACA) requires health plans to cover recommended preventive services without charging a deductible, copayment, or coinsurance. Under the ACA, the bivalent and quadrivalent HPV vaccines are covered for adolescents and young adults of either sex, and over time, ACA implementation should improve HPV vaccination rates in the United States.

Ultimately, strong vaccine recommendations from primary care providers and pediatricians are the key to HPV vaccine uptake.[76] Provider-level barriers include the lack of time to educate patients and their parents during an office visit. The United States does not have school-based vaccination programs, and patients are dependent on health care providers to promote and administer the vaccine. In a study from the 2012 National Immunization Survey–Teen, 84% of unvaccinated adolescent girls reported a health care provider encounter where they received a vaccine other than the HPV vaccine.[52] These costs and missed opportunities are significant contributors to nonvaccination.

HPV VACCINATION: RESEARCH NEEDS

The duration of efficacy is an important aspect of HPV vaccination, because the risk of acquiring HPV persists throughout a woman's or man's life. Additional research is needed to evaluate duration of protection to determine if booster doses are required. It should also be determined if there is any benefit to receiving the nine-valent HPV vaccine among those who have completed an HPV vaccination series with one of the previously available vaccines. In addition, initial studies were conducted in young adult populations, and the efficacy of these vaccines in pre- and early adolescents should be confirmed. Cost-effectiveness analyses of administration of different types (bivalent, quadrivalent, and nine-valent) and schedules (two *v* three shots) are needed, especially in low-resource settings. Because of the potential for reduced costs and improved compliance, there is growing interest in confirming whether a single- or two-dose vaccine regimen is as effective as the currently recommended three-dose regimen. A recent retrospective review of two large clinical trials noted that women who received one dose of bivalent vaccine would likely be sufficiently protected from the majority of CINs and resultant cervical cancers on the basis of their observed immunogenicity.[77] Among girls who received two doses of HPV vaccine 6 months apart, responses to HPV 16 and 18 1 month after the last dose were noninferior to those among young women who received three doses of the vaccine within 6 months.[78]

RECOMMENDATIONS FOR INCREASING UPTAKE OF HPV VACCINATION FOR CANCER PREVENTION

There is no shortage of data, experience, or examples of improved HPV vaccination uptake at the individual, local, or nationwide level. Consistent with the mission of ASCO and the aforementioned data, ASCO strongly supports efforts to markedly increase the proportion of boys and girls receiving the HPV vaccine in the United States and worldwide. We support the evidence-based recommendations of the CDC and WHO and the Healthy People 2020 goal[55] of 80% of eligible individuals completing HPV vaccination. ASCO implores the health care provider community, health care systems, municipalities, regional and national entities,

and countries to quickly incorporate strategies that have been proven to increase HPV vaccination. Specific recommendations are detailed in this section and in Table 4.

Education and Awareness Among Health Care Professionals, Policymakers, Patients, and the Public

Public and professional education. ASCO endorses the dissemination of evidence-based information to the public, professionals, and policymakers that increases awareness of the relationship between HPV and cancer at multiple sites affecting men and women. This communication should promote a shared understanding of the safety and effectiveness of available vaccines in preventing HPV infection and development of precancerous lesions that lead to cancer. Information provided to parents and caregivers should stress that the goal of HPV vaccination is to prevent cancer and that HPV vaccine effectiveness is improved with administration at age 11 to 12 years (because of greater immune response at a younger age and vaccination before HPV exposure through sexual activity)[22] as compared with after age 18 years. It should also be stated there is little to no evidence that HPV vaccination is associated with subsequent increased sexual activity.[79]

Clinical service delivery improvement. The health care community should understand and act on evidence indicating that uptake rates could be improved significantly, without compromising effectiveness, by providing the HPV vaccine along with other recommended vaccines (eg, Tdap and meningococcal virus) for young adolescents at the same time (ie, bundling).[52,80,81] A clear, strong recommendation from the health care professional providing care is the most important factor associated with vaccine delivery in a clinical setting and is essential.[82] Culturally relevant approaches should be used to reach underserved racial/ethnic groups.[83] The use of reminder or recall systems and follow-up systems supported by electronic health records, standing orders, and readily available patient education materials should be considered.

Table 4. ASCO Recommendations for Increasing HPV Vaccination

Recommendation
Education and awareness
Disseminate evidence-based information to the public, professionals, and policymakers to increase awareness of relationship between HPV and cancer.
Promote shared understanding of safety and effectiveness of available vaccines in preventing HPV infections and development of precancerous lesions (with expected reduction in HPV-caused cancers).
Clinical service delivery improvements
Promote (and bundle) HPV vaccine with other recommended vaccines for young adolescents.
Provide clear, strong recommendation for vaccine to patients, using culturally relevant approaches.
Consider use of reminder or recall systems, follow-up systems, and readily available patient education materials.
Coverage, access, and incentives for vaccination
Consider delivery through primary care medical home, alternative health-related entities (eg, pharmacies), and voluntary or mandatory school-based vaccination programs.
Adequate payment and reimbursement for delivery of vaccinations should be provided through private and government-based insurance and state-based Vaccines for Children programs.
Continue limiting out-of-pocket costs as part of Patient Protection and Affordable Care Act.
Advise patients of industry-sponsored free vaccine programs when available.
Research
Increase research to advance prevention of HPV-related cancers, with focus on what is needed to improve vaccination programs.
Continue to monitor safety and effectiveness of HPV vaccines, with periodic reassessments of their impact on prevalence of HPV infections, precancers, and invasive cancers.
Additional research is needed on relationship of antibody levels with number of immunizations needed, duration of immunity conferred, and effect of age of immunization.
Cost-effectiveness analyses of administration of different types (bivalent, quadrivalent, and nine-valent) and schedules (two *v* three shots) are needed.
Role of oncology providers
Stay abreast of established guidelines from CDC and WHO regarding HPV vaccination and recommend vaccine to patients when appropriate.
Use interactions with patients, primary care colleagues, and health care system to raise awareness of HPV-related cancers and role of vaccination in avoiding them.
Serve as community educators to disseminate evidence-based information and combat misconceptions concerning safety and effectiveness of HPV vaccine.
Advocate and actively promote policy change to increase HPV vaccination uptake.

Abbreviations: CDC, Centers for Disease Control and Prevention; HPV, human papillomavirus.

Promote Coverage of, Access to, and Incentives for Routine Vaccination

ASCO strongly endorses initiatives to improve ease of access to vaccination services and limiting out-of-pocket costs (time and money) both nationally and internationally, because vaccination rates are strongly related to these factors. The literature documents multiple measures that have resulted in increased vaccination rates for HBV and/or HPV vaccines. These include emphasizing delivery through the primary care medical home, vaccinations provided by alternate health-related entities (eg, local pharmacies), and voluntary and mandatory school-based vaccination programs. The literature documents the most consistently successful measure to ensure increased pediatric vaccination rates, including HPV and HBV vaccines, has been school-based programs, both in the United States and internationally.[52,81] Adequate payment and reimbursement for delivery of vaccinations should be provided through private and government-based health insurance and through state-based Vaccines for Children programs for those in low-income settings. Limiting out-of-pocket costs to individuals and families should be continued as part of the ACA for those with commercial insurance. Access to the vaccine is improved when barriers to payment by out-of-network or nonphysician providers are addressed. Coverage under Medicaid and Vaccines for Children programs should continue and be expanded when possible. Patients should be advised of industry-sponsored free vaccine programs when applicable.

Build and Foster Research

ASCO supports increased research to advance prevention of HPV-related cancers, with a focus on what is needed to improve how vaccination programs are implemented to enhance delivery and uptake. Monitoring and evaluation of the safety and effectiveness of HPV vaccines should continue, with periodic reassessments of their impact on the prevalence of HPV infections,

precancers, and invasive cancers. Further research should focus on the relationship of antibody levels and the number of immunizations delivered, as well as the duration of immunity conferred. The effect of immunization at earlier ages, including infancy, should be examined. Cost effectiveness, particularly in low-resource settings, is needed to inform public policy development. Additional investigation to improve implementation of vaccine programs and dissemination of the vaccine as a cancer-prevention tool is warranted. Investigations of potential therapeutic vaccines and topical microbicide agents have been initiated through the National Cancer Institute.[84,85]

Role of Oncology Providers in HPV Vaccination

Oncologists managing children, adolescents, and young adults up to age 26 years with cancer should be aware of established HPV vaccine guidelines from the CDC and WHO regarding immune-compromised individuals and can safely recommend HPV vaccination along with other recommended vaccines for their patients when appropriate. ASCO believes oncologists can play a vital role in increasing the uptake of HPV vaccines. Although most oncologists will not be direct providers of these preventive measures, this does not abrogate us from contributing to this process. Our unassailable role in the mission to lessen the burden of cancer for our patients, their families, and our communities places us in a position of influence. We should use interactions with our patients, primary care colleagues, and health care systems to raise awareness of HPV-related cancers and the role of vaccination in preventing them. Oncology providers have a responsibility to serve as community educators, disseminating evidence-based information to combat misconceptions concerning the safety and effectiveness of the HPV vaccine. ASCO encourages oncologists to advocate for and actively promote policy change to increase vaccination uptake.

DISCUSSION

Cervical cancer is one of the most common yet most preventable cancers among women living in low- and middle-income countries, and its incidence, prevalence, and mortality are aggravated by a lack of sustainable cervical cancer screening programs in these countries. In high-income countries, HPV-related cancers, including oropharyngeal and anal cancers, are on the rise in men and women. In low-, middle-, and high-income countries, the application of system-wide programs for HBV vaccination and resultant reduction of HCC rates provide pertinent examples of successful application and resultant strong value (ie, hundreds of thousands of lives saved). Both bivalent and quadrivalent HPV vaccines have been demonstrated to reduce HPV-related infection and incidence of precancerous lesions. The newly approved Gardasil-9 vaccine has expanded the coverage to the nine most common HPV types causing cancer, with the likely ability to prevent 90% of cervical cancers and 78% of anal cancers. As an organization that is committed to conquering cancer through research, education, prevention, and delivery of high-quality patient care, ASCO seeks to help reduce the burden of HPV-related cancers globally. ASCO emphasizes that the discussion regarding HPV vaccination should focus on its primary purpose: cancer prevention. To realize this achievable goal, the prophylactic HPV vaccines need to be administered effectively and widely. Therefore, ASCO is stressing to our oncology community, the global health community, and local and national policymakers the need to increase the proportion of adolescent boys and girls receiving the HPV vaccine. Data from studying HPV and other vaccines strongly support the ability to increase HPV vaccination rates through improved education, reduced cost, better provider reimbursement, more structured vaccination programs, increased involvement of oncologists in advocating the aforementioned and additional research, which could lead to complete eradication of HPV-related cancers in men and women.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

American Society of Clinical Oncology Statement: Human Papillomavirus Vaccination for Cancer Prevention

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