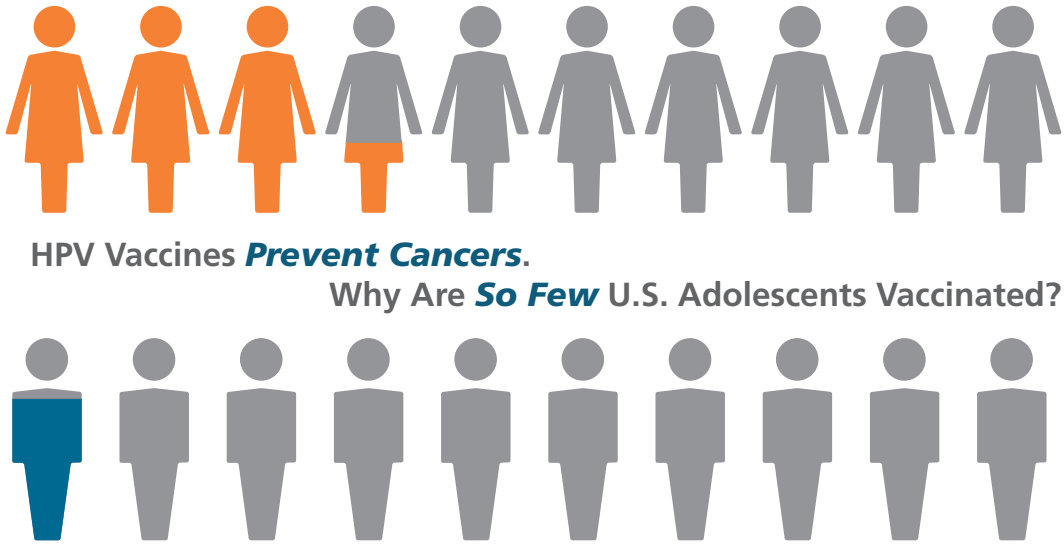
Accelerating HPV Vaccine Uptake:

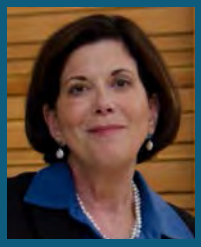
Urgency for Action to Prevent Cancer



A Report to the President of the United States

from

The President's Cancer Panel



The President's Cancer Panel

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This report is submitted to the President of the United States in fulfillment of the obligations of the President's Cancer Panel to appraise the National Cancer Program as established in accordance with the National Cancer Act of 1971 (P.L. 92-218), the Health Research Extension Act of 1987 (P.L. 99-158), the National Institutes of Health Revitalization Act of 1993 (P.L. 103-43), and Title V, Part A, Public Health Service Act (42 U.S.C. 281 *et seq.*).

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Cover graphic: Data are for U.S. adolescent males and females ages 13-17 years in 2012 who received three doses of HPV vaccine. Source: Centers for Disease Control and Prevention. National and state vaccination coverage among adolescents aged 13-17 years—United States, 2012. MMWR. 2013 Aug 30;62(34):685-93.

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

The President
The White House
Washington, DC 20500

Dear Mr. President,

Your President's Cancer Panel (the Panel) has exciting news to report to you. Our annual report details one of the most profound opportunities in cancer prevention today. Rarely will you receive a report describing the potential to eliminate certain types of cancer from our children's future. That is the focus of this report.

One in four people in the United States—nearly 80 million—are infected with at least one type of human papillomavirus (HPV), a group of viruses linked to multiple cancers and other diseases. Today, we have two safe and effective vaccines that prevent infection by the two most prevalent cancer-causing HPV types. However, in 2012, only 33 percent of adolescent females and less than 7 percent of males across the U.S. had completed the three-dose series. These low vaccination rates reveal countless missed opportunities to prevent cancers and other serious diseases. HPV vaccines are underused not only in the U.S. but around the world. The Panel finds this a serious threat to progress against cancer. We are confident that vaccine uptake can be increased dramatically, starting now, if HPV vaccination is made a public health priority by many different organizations. We believe there is the will to do that.

During 2012-2013, the Panel explored underuse of HPV vaccines and ways to accelerate vaccine uptake and protect today's children as well as future generations against cancers caused by HPV. We sought the input of diverse stakeholders, including government and nongovernmental organization leaders, researchers, healthcare providers, public health professionals, advocates, and health communication experts. We also heard compelling testimony from survivors who have lived with the physical, emotional, and financial burdens of cancers caused by HPV. Through four workshops, we identified barriers to HPV vaccine uptake and discussed steps to overcome them, with the goal of increasing HPV vaccination rates regionally, nationally, and globally.

HPV vaccines prevent cancer, so why are HPV vaccination rates as low as 12 percent in some regions of the country? The most important barriers identified among healthcare providers, parents/caregivers, and adolescents were missed clinical opportunities, misinformation, mistrust, lack of knowledge, insufficient access and/or system gaps, and cost concerns.

In this report, we provide concrete, targeted, and actionable recommendations—supported by evidence and input from key stakeholders—to address these barriers and achieve greater uptake of HPV vaccines by both boys and girls. Your Panel is proud of this report and hopes for aggressive implementation of our recommendations for supporting widespread HPV vaccination programs throughout the U.S. and the world.

We ask for your help in making this issue a priority on the Nation's public health agenda and in encouraging and facilitating mobilization of many communities around this critical public health issue. Your Panel urges you to take a visible, public stand in encouraging vaccination of age-appropriate children, adolescents, and young adults. Mr. President, your support of widespread HPV vaccination starting today can help save thousands, and perhaps hundreds of thousands, of lives and could forever alter the landscape for cancers related to HPV. No man or woman should have to suffer or die from cancers or other diseases when the means by which to protect them is within our grasp.

Sincerely,

Barbara K. Rimer, DrPH Hill Harper, JD Owen N. Witte, MD

Acknowledgments

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Table of Contents

Executive Summary

Nearly 80 million people in the U.S.—1 in every 4—are infected with at least one strain of human papillomavirus (HPV), a group of over 100 infectious agents. In most people, the body is able to clear the virus, but persistent infection with certain types of HPV is associated with multiple cancers and several other diseases.

Two safe and effective vaccines are available to protect against infection with the two most prevalent cancer-causing HPV types. Widespread vaccination against HPV could sharply reduce the number of cervical and other cancers and conditions caused by the virus. But this goal will be achieved only if HPV vaccine uptake increases dramatically. With the numbers of some HPV-associated cancers rising, we cannot afford to wait to protect our young people from future HPV infections.

In 2012-2013, to energize efforts to reach the HPV vaccines' potential to save lives, the President's Cancer Panel aimed to develop a multipronged strategy to accelerate vaccine uptake in the United States and globally. By supporting HPV vaccination as an urgent national and global health priority, the U.S. National Cancer Program has an unprecedented opportunity to contribute to preventing millions of avoidable cancers and other conditions in men and women worldwide.

Part 1: The Case for HPV Vaccination

Worldwide, about 2 million new cancer cases are caused by infectious diseases every year. More than 600,000 of these are caused by human papillomaviruses.

The vast majority of HPV infections are cleared by the immune system within two years. However, if the virus is not cleared, certain HPV types can cause abnormal growths, including several cancers, genital warts, and noncancerous but serious tumors in the respiratory tract called recurrent respiratory papillomatosis (RRP). Cervical cancer is the most common cancer caused by HPV, although the viruses also play a significant role in cancers of the vulva, vagina, anus, penis, and oropharynx.

The discovery that infectious agents can cause cancers opened the door for a new cancer prevention strategy—vaccination. Vaccines against infectious agents have been one of the greatest success stories in public health, leading to eradication of smallpox and drastically reducing the incidence and severity of many other deadly diseases attributable to infectious agents.

Vaccines capable of preventing cancers have been a goal for many years, but until recently, only one had been developed—a vaccine against hepatitis B, a leading cause of liver cancer.

Two vaccines—Cervarix® and Gardasil®—are approved by the U.S. Food and Drug Administration (FDA) to prevent several HPV-associated diseases. These vaccines prevent infections by the two most prevalent types of cancer-causing HPV: HPV16 and HPV18. Together, these types are responsible for more than 400,000 cases of cancer around the world each year, including 22,000 in the United States. Gardasil® also prevents infection by two types of HPV that cause genital warts and RRP: HPV6 and HPV11.

The vaccines are recommended by the U.S. Advisory Committee on Immunization Practices (ACIP) for males and females ages 11-12 with "catch-up" doses for females up to age 26 and for males up to age 21 who were not vaccinated earlier in adolescence. Receiving the HPV vaccine at ages 11-12 offers earlier protection against infection, and immune response to the vaccine is better in younger age groups than among older women and men.

Part 2: Urgency for Action

HPV vaccine uptake has not kept pace with that of other adolescent vaccines and has stalled in the past few years. In 2012, only about one-third of 13- to 17-year-old girls received all three recommended doses. These levels fall considerably short of the U.S. Department of Health and Human Services *Healthy People 2020* goal of having 80 percent of 13- to 15-year-old girls fully vaccinated against HPV. Immunization rates for U.S. boys are even lower than for girls. Less than 7 percent of boys ages 13 to 17 completed the series in 2012. This low rate is in large part because the ACIP recommendation for routine vaccination of boys was not made until 2011. However, it is even lower than what was observed for girls in 2007—the first year following the recommendation for females—suggesting that concerted efforts are needed to promote HPV vaccination of males.

The Centers for Disease Control and Prevention (CDC) estimates that increasing HPV vaccination rates from current levels to 80 percent would prevent an additional 53,000 future cervical cancer cases in the United States among girls who now are 12 years old or younger over the course of their lifetimes. Thousands of cases of

other HPV-associated cancers in the U.S. also likely would be prevented within the same timeframe. A growing proportion of these cancers—most notably, oropharyngeal cancers—will occur in males, who currently are vaccinated at very low rates.

The President's Cancer Panel finds underuse of HPV vaccines a serious but correctable threat to progress against cancer. Organized, mutually reinforcing efforts could have synergistic impact on HPV vaccine uptake. The Panel presents four goals to increase HPV vaccine uptake; three goals focus on increasing uptake in the United States (Part 3), and the fourth addresses ways the United States can help increase global uptake of the vaccines (Part 4). Several high-priority research areas also are identified (Part 5). All recommendations and some of the stakeholders responsible for implementing them are summarized in Appendix B. The Panel urges all stakeholders—including federal and state governments, healthcare professionals, nongovernment organizations with a focus on public health, and parents, caregivers, adolescents, and other members of the public—to contribute to efforts to achieve this goal and protect millions of men and women around the world from the burden of avoidable cancers and other diseases and conditions in the coming years.

Part 3: Accelerating HPV Vaccine Uptake in the United States

The Panel recommends three critical goals that must be achieved to increase HPV vaccine uptake in the United States, with the ultimate goal being completion of the full three-dose vaccine series by all age-eligible adolescents for whom the vaccine is not contraindicated.

GOAL 1: REDUCE MISSED CLINICAL OPPORTUNITIES TO RECOMMEND AND ADMINISTER HPV VACCINES

According to CDC, missed clinical opportunities are the most important reason why the U.S. has not achieved high rates of HPV vaccine uptake. Many vaccine-eligible adolescents do not receive HPV vaccines during visits with their healthcare providers. As many as two-thirds of 11- and 12-year-old vaccine-eligible girls may not be receiving HPV vaccines at visits at which they receive at least one other vaccine.

Targeted efforts should be made to address factors that keep providers from strongly recommending HPV vaccines. Overcoming these obstacles could substantially reduce the number of missed opportunities to recommend and administer HPV vaccines.

Objective 1.1: CDC should develop, test, disseminate, and evaluate the impact of integrated, comprehensive communication strategies for physicians and other relevant health professionals.

Objective 1.2: Providers should strongly encourage HPV vaccination of age-eligible males and females whenever other vaccines are administered.

Objective 1.3: Healthcare organizations and practices should use electronic office systems, including electronic health records (EHRs) and immunization information systems (IIS), to avoid missed opportunities for HPV vaccination.

Objective 1.4: Healthcare payers should reimburse providers adequately for HPV vaccines and for vaccine administration and services.

Objective 1.5: The current Healthcare Effectiveness Data and Information Set (HEDIS) quality measure for HPV vaccination of adolescent females should be expanded to include males.

Objective 1.6: Create a *Healthy People 2020* HPV vaccination goal for males.

GOAL 2: INCREASE PARENTS', CAREGIVERS', AND ADOLESCENTS' ACCEPTANCE OF HPV VACCINES

Parents' and other caregivers' knowledge, attitudes, and beliefs affect whether their children receive vaccines, including HPV vaccines. Most parents believe that vaccines protect their children from potentially life-threatening diseases, but some refuse one or more recommended vaccines based on concerns about safety and other factors.

Studies have provided insight into parents' views, including that parents are more likely to refuse HPV vaccines than other recommended vaccines and that parents of young adolescents may feel that they can wait to vaccinate their children against HPV. Targeted efforts should be made to increase HPV vaccine acceptance among parents, caregivers, and adolescents.

Objective 2.1: CDC should develop, test, and collaborate with partner organizations to deploy integrated, comprehensive communication strategies directed at parents and other caregivers, and also at adolescents.

GOAL 3: MAXIMIZE ACCESS TO HPV VACCINATION SERVICES

Vaccines should be available where adolescents receive healthcare. It should be convenient to initiate and complete the HPV vaccine series, and cost should not be a barrier.

Medical homes are the optimal environment for administering HPV vaccines, particularly the first dose, because medical homes provide opportunities to

educate parents and adolescents and to deliver other important preventive care services. Reducing missed clinical opportunities for HPV vaccination in medical homes will go a long way toward increasing HPV vaccine uptake. However, the Panel recognizes that providing additional venue choices may increase the likelihood that adolescents will receive all three doses of HPV vaccine. Therefore, the Panel recommends increasing the range of venues and providers for HPV vaccination.

Objective 3.1: Promote and facilitate HPV vaccination in venues outside the medical home.

Objective 3.2: States should enact laws and implement policies that allow pharmacists to administer vaccines to adolescents, including younger adolescents.

Objective 3.3: Overcome remaining barriers to paying for HPV vaccines, including payment for vaccines provided outside the medical home and by out-of-network or nonphysician providers.

Part 4: Increasing Global HPV Vaccination

The burden of HPV-associated cancers extends beyond the borders of the United States, affecting populations in every country. Patterns of HPV-associated cancers differ by region. Cervical cancer is the most common HPV-associated cancer globally. In less developed regions, the large majority of HPV-attributed cancers are cervical cancers. In the United States and other more developed regions, other sites account for a significant proportion of HPV-associated cancers.

While the prevalence of HPV infections and distribution of HPV types vary by region, research has found consistently that HPV16 and HPV18, the cancer-causing strains HPV vaccines protect against, are responsible for at least two-thirds of cervical cancer cases in populations around the world. This provides a strong indication that HPV vaccines will be effective virtually everywhere.

As with cervical cancer screening programs, HPV vaccination programs have been implemented primarily in high-resource areas. Some of the most successful vaccination programs are in Australia, the United Kingdom, and parts of Canada. The U.S. can learn from successful HPV vaccination programs in these and other countries that in some cases have already led to measurable public health benefits.

Addressing the global burden of HPV-associated cancers requires implementation of HPV vaccination programs in low- and middle-income countries, where the majority of HPV-associated cancer cases occur.

GOAL 4: PROMOTE GLOBAL HPV VACCINE UPTAKE

The World Health Organization recommends that HPV vaccines be introduced into national immunization programs where prevention of cervical cancer is a public health priority and vaccine introduction is feasible and sustainable. The Panel recommends that the United States collaborate with global partners to support HPV vaccine uptake and other cancer prevention and control activities worldwide.

Objective 4.1: The United States should continue its collaboration with and support of GAVI to facilitate HPV vaccine introduction and uptake in low-income countries.

Objective 4.2: The United States should continue to support global efforts to develop comprehensive cancer control plans and cancer registries in low- and middle-income countries.

Part 5: High-Priority Research to Advance Prevention of HPV-Associated Cancers

HPV vaccines and their public health benefits were enabled by decades of laboratory, clinical, and population-based research. Additional research in several areas could increase the impact of HPV vaccination. Confirmation that extended dosing schedules and/or fewer vaccine doses adequately protect against HPV infections would have enormous implications for HPV vaccine programs in both high- and low-resource settings. Other areas of investigation include improved ways to communicate about HPV vaccines. Finally, it is not too early to anticipate the time when HPV vaccination is disseminated widely across populations and to ask how cervical cancer screening guidelines will need to be changed.

High-Priority Research Areas

- Investigate more convenient dosing schedules for current vaccines.
- Develop next-generation vaccines that provide broader protection and/or are easier to store and administer.
- Explain the natural history of oropharyngeal HPV infections.
- Develop more effective ways to communicate about HPV-associated diseases and HPV vaccines.
- Determine how best to integrate HPV vaccination with cervical cancer screening.

Preface

The President's Cancer Panel (PCP, the Panel), established by the National Cancer Act of 1971 (P.L. 92-218), is charged with monitoring progress of the National Cancer Program and identifying barriers to its fullest and most rapid implementation. The Panel investigates topics of high importance to the National Cancer Program, collecting information through a series of meetings and additional information gathering. Findings and recommendations are compiled in reports to the President of the United States. While reports are *to* the President, they are also *for* a larger group of stakeholders, public and private, that comprise the National Cancer Program. Together, these organizations and others can make a positive difference in accelerating progress against cancer.

For its 2012-2013 series, the Panel chose to focus on human papillomavirus (HPV) vaccines, with the goal of catalyzing stakeholders to accelerate uptake of these effective but underused interventions to prevent cancers and other diseases and conditions caused by HPV. Such a significant opportunity to prevent cancers in the U.S. and around the world is rare. The Panel convened four workshops on HPV vaccination to gather information from many stakeholders in this area, including representatives from the public, academic, nongovernmental, and private sectors with expertise and responsibility in HPV-associated cancer research, vaccine-related public health policy, and vaccine program development and implementation. Three workshops focused on HPV vaccination in the United States. The fourth focused on issues related to global HPV vaccination. (See Appendix A for more information on the workshops.)

HPV-associated cancers are life-threatening, and the incidence of some is increasing in the United States and many other countries. Many of these cancers are preventable by HPV vaccines. The U.S. Advisory Committee on Immunization Practices (ACIP) recommends HPV vaccination for adolescents and young adults. This recommendation has been endorsed and/or echoed by the National Cancer Institute (NCI), the Centers for Disease Control and Prevention (CDC), and numerous U.S. medical professional societies and other organizations.* Increased uptake of HPV vaccines for females also is an objective of the U.S. Department of Health and Human Services *Healthy People 2020* initiative.[1-6] The World Health Organization (WHO) recommends that HPV vaccines be integrated into national immunization programs whenever possible.[7]** Panel members communicated with representatives of many of these organizations and were impressed by their commitment to increase uptake of HPV vaccines.

Despite strong recommendations from experts in the medical and public health fields, rates of U.S. HPV vaccination have fallen short of target levels. It will take concerted action by multiple individuals and organizations to increase HPV vaccine uptake. In this report, the Panel presents high-priority goals and objectives that stakeholders should embrace to increase uptake of HPV vaccines. In many cases, these recommendations call for implementation of strategies shown to be effective for increasing uptake of other vaccines.[8] The Panel's recommendations are consistent with those issued by the National Vaccine Advisory Committee (NVAC) for improving uptake of vaccines in general[9] and adolescent vaccines in particular.[10,11] The U.S. National Cancer Program, in aggregate, has a major opportunity to accelerate uptake of HPV vaccines in the United States and support their adoption around the world. The Panel believes that concerted action could create a tipping point that would lead to large increases in HPV vaccine uptake. The potential to prevent cervical and other cancers on a global scale is achievable.

* These include the American Academy of Family Physicians, American Academy of Pediatrics, American Cancer Society, American College of Obstetricians and Gynecologists, and Society for Adolescent Health and Medicine. See Appendix C for more information on HPV vaccine recommendations, endorsements, and goals.

** WHO recommends that routine HPV vaccination be included in national immunization programs if: (1) prevention of cervical cancer and/or other HPV-related diseases is a public health priority, (2) vaccine introduction is programmatically feasible, (3) sustainable financing can be secured, and (4) cost-effectiveness of vaccination strategies is taken into account.

PART 1
THE CASE FOR HPV VACCINATION

Worldwide, about 2 million new cancer cases are caused by infectious diseases every year.[12] More than 600,000 of these are caused by human papillomaviruses (Figure 1), viruses common in the U.S. and around the world. The discovery that infectious agents can cause cancers opened the door for a new cancer prevention strategy—vaccination. Vaccines against infectious agents have been one of the greatest success stories in public health, leading to eradication of smallpox and drastically reducing the incidence and severity of many other deadly diseases attributable to infectious agents. Vaccines capable of preventing cancers have been a goal for many years, but until recently, only one had been developed—a vaccine against hepatitis B virus, a leading cause of liver cancer.

HPV vaccines provide an effective, safe means to prevent diseases caused by some of the most dangerous types of HPV: HPV16 and HPV18. Together, these two HPV types are responsible for more than 400,000 cases of cancer around the world each year (Table 1), including 22,000 in the United States (Table 2). Yet, in the U.S., only one-third of adolescent girls and less than 7 percent of adolescent boys have received all three recommended vaccine doses.[13]

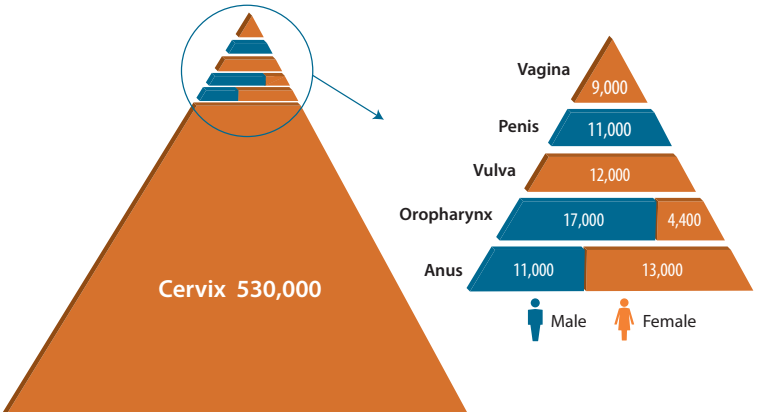
The President's Cancer Panel finds underuse of HPV vaccines a serious, but correctable threat to progress against cancer.

Millions in the U.S. Are Infected with HPV

Nearly 80 million people in the U.S.—1 in every 4 people—are infected with at least one strain of HPV.[14,15] HPV is the most common sexually transmitted infection in the United States. Of the more than 100 types of HPV that have been identified, at least 40 can infect the genital areas, mouths, and throats of both males and females. Almost all sexually active men and women will be infected at some point in their lives, even those who have had sex with only one other person.[15]

Most HPV types pose little risk, and the vast majority of HPV infections (about 90%) are cleared by the immune system within two years. However, if the virus is not cleared, certain HPV types can cause health problems, including several types of cancer, genital warts, and noncancerous but serious tumors in the respiratory tract called recurrent respiratory papillomatosis (RRP).

Figure 1
Numbers of Cancers Caused by HPV Worldwide Each Year



Note: Global estimates of genital warts and recurrent respiratory papillomatosis incidence are not available.
Source: de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol. 2012;13(6):607-15.

HPV Infections Cause Thousands of Cancers and Other Conditions Each Year in the U.S.

HPV infections are responsible for nearly 26,000 new cancer cases each year in the United States. Of these, 18,000 occur in women and 8,000 occur in men (Figure 2).[16] (See *How HPV Infections Cause Cancers* on page 5 for more information on the progression from HPV infection to cancer.) HPV also causes more than 300,000 cases of genital warts and approximately 820 cases of juvenile-onset RRP in the U.S. each year.[17,18]* The combined cost of HPV-associated cancers and other conditions is estimated to be $8 billion per year in the United States.** A large majority of cancers caused by HPV are brought about by one of two types: HPV16 or HPV18 (Table 2). Together, these types cause about 22,000 cases of cancer in the United States each year.

Cervical cancer is the most common cancer caused by HPV. Almost all cases of cervical cancer—which kills 4,000 U.S. women each year[19]—are caused by HPV infections. Although cervical cancer is the cancer most commonly associated with HPV, the virus plays a significant role in other anogenital cancers in both men and women. These include cancers of the vulva, vagina, and anus in women and cancers of the anus and penis in men.[16,20]

HPV-associated cancers of the oropharynx (the part of the throat just behind the mouth) are a growing problem in the United States and many other high-

Table 1
Cancers Attributed to HPV Worldwide

Cancer Site	Number of Cancers Probably Caused by HPV (a)	Percent of HPV-Associated Cancers Probably Caused by HPV16 or 18 (b)	Number of Cancers Probably Caused by HPV16 or 18
Anus	24,000	92	22,100
Cervix	530,000	70	371,000
Oropharynx	22,000	89	19,600
Penis	11,000	63	6,900
Vagina	9,000	80	7,200
Vulva	12,000	80	9,600
TOTAL	**608,000**		**436,400**

(a) de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol. 2012;13(6):607-15.
(b) Gillison ML, Chaturvedi AK, Lowy DR. HPV prophylactic vaccines and the potential prevention of noncervical cancers in both men and women. Cancer. 2008;113(10 Suppl):3036-46.

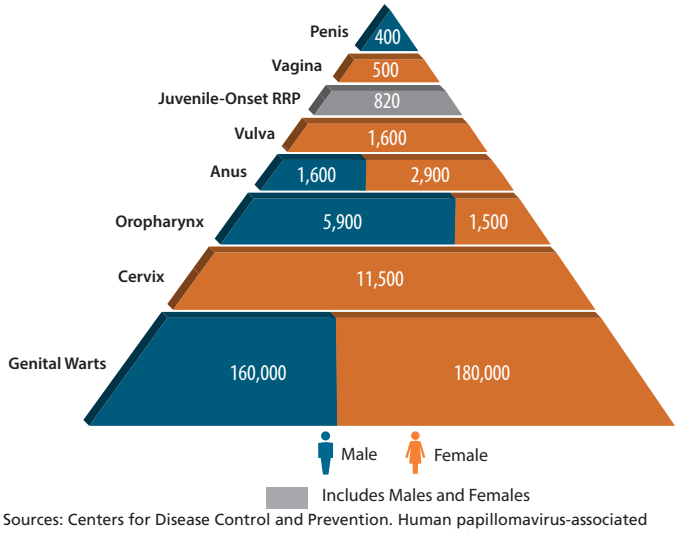
* Data on incidence of adult-onset RRP are not available.
** Includes costs of cervical cancer screening and follow-up and the treatment costs of cervical, anal, vaginal, vulvar, penile, and oropharyngeal cancers, as well as genital warts and RRP.

Table 2
U.S. Cancers Attributed to HPV

Cancer Site	Average # Cancers Per Year at Site (a)	Percent Probably Caused by HPV (a)	Number Probably Caused by HPV (a)	Percent HPV Cancers Probably Caused by HPV16 or 18 (b)	Number of Cancers Per Year Probably Caused by HPV16 or 18
Anus	4,767	93	4,500	93	4,200
Cervix	11,967	96	11,500	76	8,700
Oropharynx	11,726	63	7,400	95	7,000
Penis	1,046	36	400	87	300
Vagina	729	64	500	88	400
Vulva	3,136	51	1,600	86	1,400
TOTAL	**33,371**		**25,900**		**22,000**

(a) Centers for Disease Control and Prevention. Human papillomavirus-associated cancers—United States, 2004-2008. MMWR. 2012 Apr 20;61(15):258-61.
(b) Gillison ML, Chaturvedi AK, Lowy DR. HPV prophylactic vaccines and the potential prevention of noncervical cancers in both men and women. Cancer. 2008;113(10 Suppl):3036-46.

Figure 2
Numbers of U.S. Cancers and Genital Warts Attributed to HPV Infections



Sources: Centers for Disease Control and Prevention. Human papillomavirus-associated cancers—United States, 2004-2008. MMWR. 2012 Apr 20;61(15):258-61; Hoy T, Singhal PK, Willey VJ, Insinga RP. Assessing incidence and economic burden of genital warts with data from a US commercially insured population. Curr Med Res Opin. 2009;25(10):2343-51; Chesson HW, Ekwueme DU, Saraiya M, Watson M, Lowy DR, Markowitz LE. Estimates of the annual direct medical costs of the prevention and treatment of disease associated with human papillomavirus in the United States. Vaccine. 2012;30(42):6016-9.

How HPV Vaccines Work

Both Gardasil® and Cervarix® are made using recombinant DNA technology. This technology is used to generate viral proteins capable of self-assembling into so-called virus-like particles (VLPs). VLPs are made for each HPV type targeted by the vaccines. HPV VLPs contain no viral genetic material and thus are not infectious but effectively mimic exposure to HPV, provoking the immune system to generate antibodies against specific types of HPV. These antibodies protect vaccinated individuals against infection with target HPV types.

Sources: Day PM, Kines RC, Thompson CD, Jagu S, Roden RB, Lowy DR, et al. *In vivo* mechanisms of vaccine-induced protection against HPV infection. Cell Host Microbe. 2010;8(3):260-70; Garland SM, Smith JS. Human papillomavirus vaccines: current status and future prospects. Drugs. 2010;70(9):1079-98.

income countries.[21] The incidence of these cancers more than tripled in the U.S. between 1988 and 2004.[22] At this rate, the number of new oropharyngeal cancer cases caused by HPV likely will exceed the number of cervical cancer cases by 2020. This shift has important public health implications, in part because oropharyngeal cancers are four times more common among men than among women (Figure 2). Thus, efforts to prevent HPV-associated diseases must focus on both females *and* males.[21]

Vaccines Prevent HPV Infections and Associated Diseases

Two vaccines—Cervarix® and Gardasil®—are approved by the U.S. Food and Drug Administration (FDA) for prevention of several HPV-associated diseases (Table 3). Cervarix® protects against the two types of HPV most commonly found in cancers: HPV16 and HPV18. In addition to protecting against these two cancer-causing HPV types, Gardasil® protects against HPV6 and HPV11. While these two forms of the virus do not cause cancers, they are responsible for most cases of genital warts and RRP. Both vaccines are highly effective at preventing HPV infections and the diseases caused by the HPV types they target. HPV16 and HPV18 cause about 75 percent of cervical cancers in the U.S. and even higher proportions of noncervical cancers associated with HPV, which implies that most HPV-associated cancers potentially could be prevented by these vaccines (Table 2).[23]

Table 3
HPV Vaccines

	Gardasil®	Cervarix®
HPV Types	6, 11, 16, 18	16, 18
Manufacturer	Merck & Co.	GlaxoSmithKline
Initial U.S. Licensing	2006	2009
Approved for Prevention of	Cervical cancer and precancers Vulvar cancer and precancers Vaginal cancer and precancers Anal cancer and precancers Genital warts	Cervical cancer and precancers
Approved for Use in	Females (9 to 26 years old) Males (9 to 26 years old)	Females (9 to 25 years old)

Sources: U.S. Food and Drug Administration. Gardasil® [Internet]. Silver Spring (MD): FDA; 2011 Oct 21 [cited 2013 Aug 1]. Available from: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM094042; U.S. Food and Drug Administration. Cervarix® [Internet]. Silver Spring (MD): FDA; 2013 Aug 1 [cited 2013 Aug 1]. Available from: http://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm186957.htm.

Clinical Trials Demonstrate HPV Vaccines' Potential

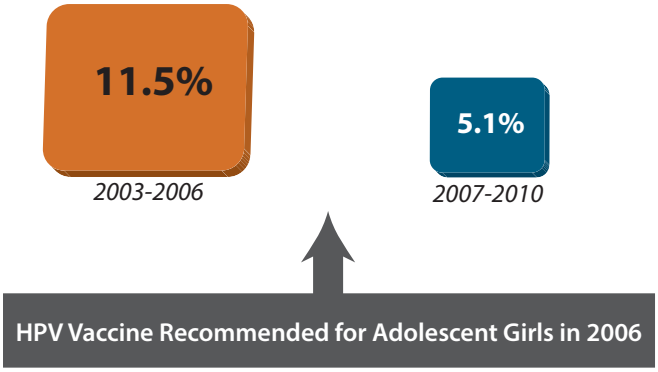
Clinical trials have shown that HPV vaccines could prevent the majority of cervical cancers if used optimally. Of 10,000 young women who were vaccinated as part of clinical trials before they were exposed to cancer-causing forms of HPV, none developed high-grade HPV16/18-associated cervical lesions, which are precursors to invasive cancer.[24,25] (See *How HPV Infections Cause Cancers* on page 5.) Since these lesions are on the pathway to cervical cancer, the striking results led experts to estimate that universal uptake of available HPV vaccines likely would prevent more than two-thirds of cervical cancers worldwide (virtually all of those caused by HPV16/18).[26] Gardasil® prevents other HPV16/18-associated anogenital precancers and HPV6/11-associated genital warts with similar efficacy.[25,27] Neither currently approved HPV vaccine is licensed for prevention of oropharyngeal cancers. However, based on what is known about the biology of this disease, it is highly likely that the vaccines will provide protection against oropharyngeal cancers.[21] Women who received Cervarix® as part of a clinical trial had much lower prevalence of oral HPV infection than participants in the trial who had not received the HPV vaccine.[28]

HPV Vaccines Already Are Benefiting Many

While clinical trial results are important, the value of the HPV vaccines depends on their effectiveness in preventing diseases in real-world settings, as is true of the impact of hepatitis B vaccines on liver cancer rates. It may take decades for the full impact of HPV vaccination on cancer rates to emerge, given the long interval between initial infection and development of invasive cancer (see *How HPV Infections Cause Cancers* on page 5). However, earlier endpoints, including HPV infection prevalence and genital warts incidence (for Gardasil®), can provide critical insight into effectiveness of the vaccines. Measuring these endpoints poses challenges. Monitoring HPV infection requires sampling from the site of infection, DNA extraction, and identification of specific HPV types. In addition, genital warts cases are not consistently reported in many countries. However, investments in these types of surveillance activities are critically important.

Data collected through surveillance have revealed dramatic declines in HPV infection rates and genital warts among vaccinated age groups in the United States, and other countries with HPV vaccine programs provide early indicators of vaccine efficacy.[29-32] In the United States, rates of cervical

Figure 3
Decline in Prevalence of HPV6, 11, 16, and 18 Among U.S. Girls Ages 14 to 19 Following HPV Vaccine Introduction



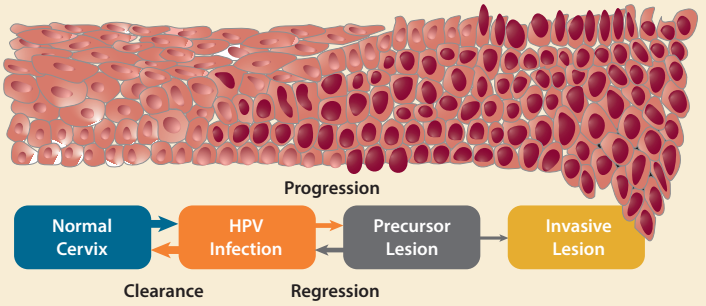
Source: Markowitz LE, Hariri S, Lin C, Dunne EF, Steinau M, McQuillan G, et al. Reduction in human papillomavirus (HPV) prevalence among young women following HPV vaccine introduction in the United States, National Health and Nutrition Examination Surveys, 2003-2010. J Infect Dis. 2013;208(3):385-93.

How HPV Infections Cause Cancers

HPV infection of cervical cells initiates a series of molecular events that sometimes, but not always, results in invasive cancer. Although less research has been done on other HPV-associated cancers, the progression from infection to cancer appears to occur through analogous processes. Many HPV infections are cleared by the immune system. Some of these transient infections result in low-grade precancerous lesions consisting of a few abnormally sized and oddly shaped cells. Many of these lesions disappear within a few months with no treatment. In some cases, persistent HPV infection causes high-grade precancerous lesions. These precancerous lesions sometimes regress spontaneously or can be treated if detected. However, some will progress to invasive cancer. The interval between cervical HPV infection and invasive cancer is usually at least 20 years; however, precancerous lesions usually develop much earlier. Detection and treatment of precancerous lesions through screening has reduced cervical cancer incidence and mortality in the United States and other high-income countries over the past several decades. HPV vaccines have potential to further reduce the burden of this disease by preventing both precancerous lesions and invasive cancers.

Sources: Woodman CB, Collins SI, Young LS. The natural history of cervical HPV infection: unresolved issues. Nat Rev Cancer. 2007;7(1):11-22; Crow JM. HPV: the global burden. Nature Outlook. 2012;488(7413):S2-3.

Figure modified from: Crow JM. HPV: the global burden. Nature Outlook. 2012;488(7413):S2-3.



infection with HPV types covered by the vaccines fell by more than 50 percent among girls 14 to 19 years of age in the four years following vaccine introduction (Figure 3). This study included both vaccinated and unvaccinated girls.[29] The decline was even more dramatic in Australia, where the national HPV program has achieved higher levels of vaccination than in the United States (see Figure 10 in Part 4). In that country, the prevalence of infections with HPV types covered by the vaccines fell by more than 75 percent among women 18 to 24 years of age.[30] The prevalence of genital warts in Australia also plummeted; a 92 percent reduction was observed among females under 21 years of age.[31]

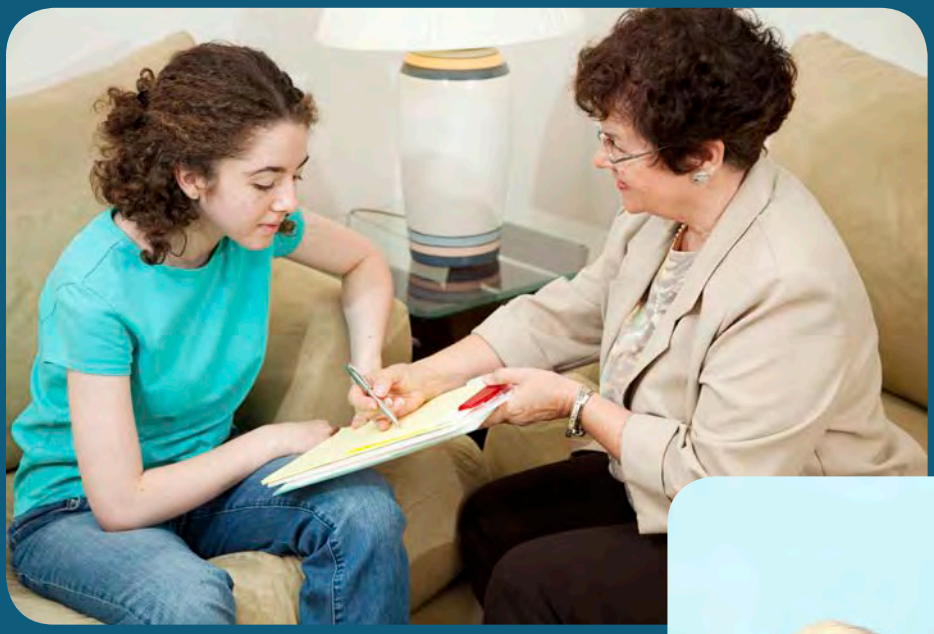
Several studies have found reductions in HPV infections and related diseases in unvaccinated populations as well as in those who have received vaccines.[30,31,33] This phenomenon is known as herd immunity. It refers to the fact that preventing HPV infections in vaccinated individuals reduces the likelihood that unvaccinated individuals will be exposed to HPV. For example, in Australia, where the HPV vaccination program has focused primarily on females, the incidence of genital warts declined more than 80 percent among heterosexual men under 21 years of age between 2007 and 2011 but did not change among men who have sex with men.[31] While herd immunity may enhance the protective benefits of vaccination programs, the best way for people to protect themselves from infection and disease is to be vaccinated themselves.

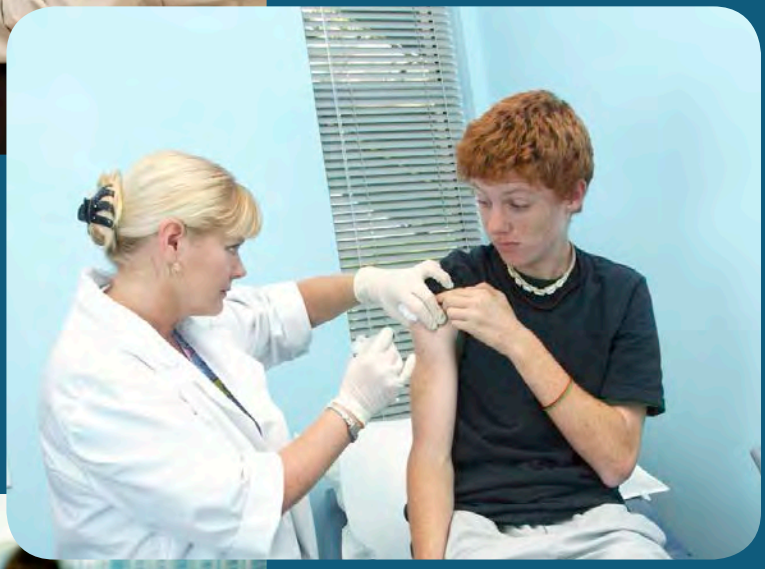
HPV Vaccines Are Safe

"Herd immunity" is the reduced incidence of infections among unvaccinated individuals. High rates of vaccination make it less likely that infections will be spread. Another term used to describe this is "community immunity."

By early 2013, more than 56 million HPV vaccine doses had been administered in the United States.[34] HPV vaccines have excellent safety profiles, similar to those of other licensed adolescent vaccines. Safety data on the vaccines are drawn from both prelicensure clinical trial data and postlicensure safety monitoring conducted by CDC, FDA, and vaccine manufacturers. While there is always the possibility for an individual to have a serious reaction to an HPV vaccine, as is the case with any medical procedure, the risk of such a reaction is extremely small. To date, three population-based safety studies have been conducted in the United States.[35-37] These studies have identified no serious safety concerns, although one observed increased risk of syncope (fainting) on the day of vaccination and skin infections in the two weeks following vaccination.[37]* The risk of syncope is not unique to HPV vaccination; immunizations in general have been linked to syncope, particularly among adolescents.[38,39] FDA and CDC continue to monitor the safety of the HPV vaccines and follow up on individual reports of serious adverse events. Additional information on safety monitoring of these vaccines can be found on the CDC website.[40]

* Skin infections are not infections with HPV (HPV vaccines do not contain live virus). Medical record review suggested that some of the reported skin infection cases may have been local injection site reactions. Other documented infections (not necessarily at injection site) included impetigo, pilonidal cyst, and carbuncle.





PART 2
URGENCY FOR ACTION

In 2006, the U.S. Advisory Committee on Immunization Practices (ACIP) recommended HPV vaccination for adolescent girls and added a similar recommendation for adolescent boys in 2011 (see sidebar on page 8).[41-43] The HPV vaccine series consists of three doses given over six months. Thus, vaccine uptake is a function of both initiation (getting the first vaccine dose) and completion (getting all three vaccine doses).

HPV Vaccines Are Underused in the U.S.

In 2007, the first full year after Gardasil® was approved in the U.S., about one-quarter of 13- to 17-year-old girls received at least one HPV vaccine dose. This is similar to the proportion who received other adolescent vaccines, such as meningococcal conjugate and Tdap vaccines, during the first year they were recommended (Figure 4).[44] However, uptake of HPV vaccines has not kept pace with that of other adolescent vaccines and has stalled in the past few years. In 2012, only 53.8 percent of 13- to 17-year-old girls had received the first HPV vaccine dose, and only 33.4 percent had completed all three recommended doses.[34] These levels are nearly identical to what was observed in 2011 and fall considerably short of the *Healthy People 2020* goal of having 80 percent of 13- to 15-year-old girls fully vaccinated against HPV.[5] They also are substantially lower than HPV vaccine coverage rates in other high-income countries, such as Australia and the United Kingdom (U.K.) (see Figure 10 in Part 4).

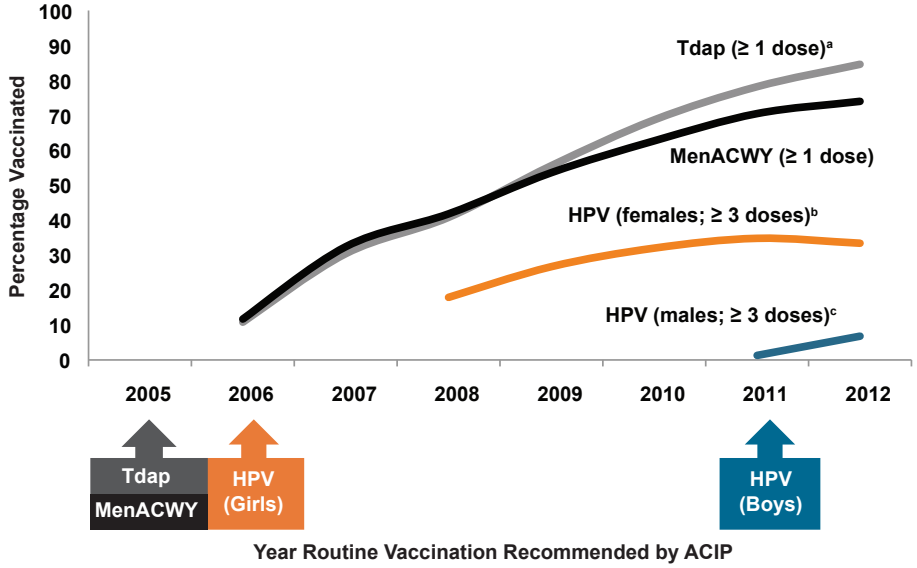
Immunization rates for U.S. boys are even lower than for girls. Only 20.8 percent of boys ages 13-17 had received at least one dose, and only 6.8 percent had completed the series, in 2012.[13] Though only one year after the ACIP recommendation for boys was issued, this rate of HPV vaccine initiation is substantially lower than that observed for girls in 2007, suggesting the need for concerted efforts to promote HPV vaccination of boys.

While informative, national HPV vaccination statistics do not reflect regional trends that may be important for HPV-associated cancer prevention efforts. Some states and regions have been more successful than

The U.S. Advisory Committee on Immunization Practices recommends:

- Routine vaccination of females ages 11 or 12 years with three doses of either Cervarix® or Gardasil®. The vaccination series can be started beginning at age 9 years. Vaccination is recommended for females ages 13 through 26 years who have not been vaccinated previously or who have not completed the three-dose series.
- Routine vaccination of males* ages 11 or 12 years with Gardasil® administered as a three-dose series. The vaccination series can be started beginning at age 9 years. Vaccination with Gardasil® is recommended for males ages 13 through 21 years who have not been vaccinated previously or who have not completed the three-dose series. Males ages 22 through 26 years may be vaccinated.

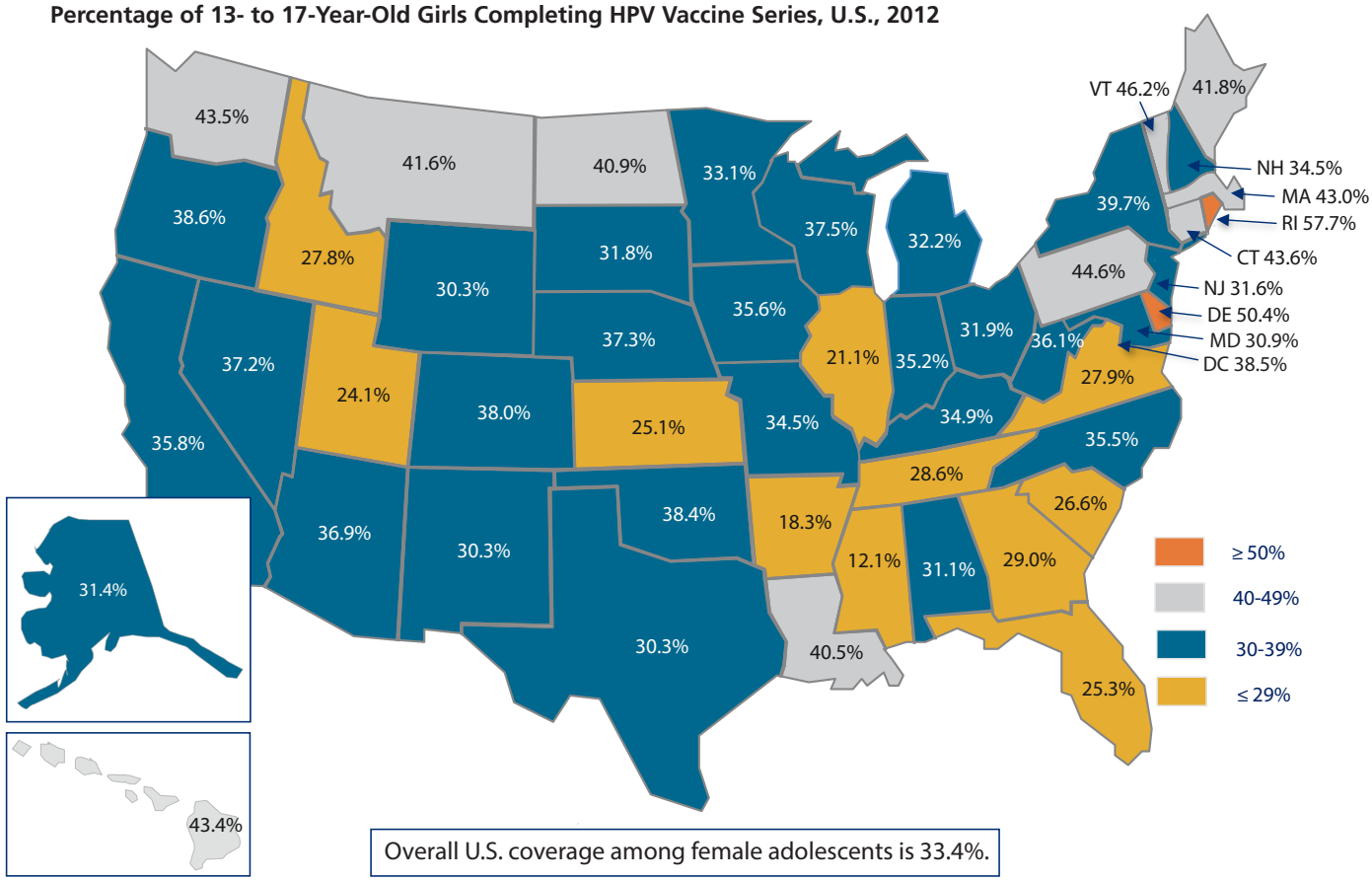
Figure 4
U.S. Uptake of Adolescent Vaccines Through 2012



ACIP = Advisory Committee on Immunization Practices; HPV = human papillomavirus; MenACWY = meningococcal conjugate; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.
(a) After age 10 years.
(b) ≥ 3 doses HPV vaccine, either Cervarix® or Gardasil®, among females. ACIP recommends either Cervarix® or Gardasil® for females.
(c) ≥ 3 doses HPV vaccine, either Cervarix® or Gardasil®, among males. ACIP recommends Gardasil® for males but some males may have received Cervarix®.
Source: Centers for Disease Control and Prevention. National and state vaccination coverage among adolescents aged 13-17 years—United States, 2012. MMWR. 2013 Aug 30;62(34):685-93.

* ACIP issued a permissive recommendation for HPV vaccination of males in 2009. This was upgraded to a routine recommendation in 2011.

Figure 5
Percentage of 13- to 17-Year-Old Girls Completing HPV Vaccine Series, U.S., 2012



Source: Centers for Disease Control and Prevention. National and state vaccination coverage among adolescents aged 13-17 years—United States, 2012. MMWR. 2013 Aug 30;62(34):685-93. Data from National Immunization Survey-Teen (NIS-Teen) among female adolescents (N = 9,058) born between January 6, 1994, and February 18, 2000. Gardasil® or Cervarix® may have been received; more than the recommended three doses may have been received.

others in achieving uptake of HPV vaccination (Figure 5). As of 2012, more than one-half of girls in only two states (Delaware and Rhode Island) had received the full HPV vaccine series, and vaccine completion was less than 30 percent in 11 states. The lowest rate of HPV vaccine series completion is 12.1 percent.[44] Of particular concern, those states with low rates of HPV vaccine uptake often also have high cervical cancer incidence and mortality rates.[45]*

Increasing HPV Vaccine Uptake Must Be a Public Health Priority

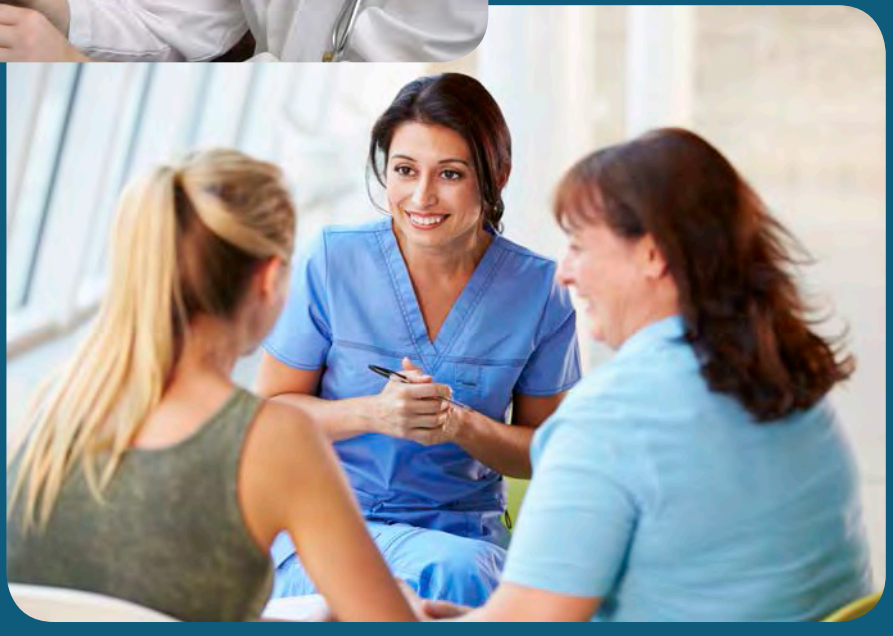
Concerted, coordinated efforts by multiple public and private organizations are needed to increase HPV vaccine uptake and achieve the vaccines' potential to prevent cancers. These efforts should promote both initiation of the first dose and completion of all three recommended doses for age-eligible adolescents, as well as young adults who have not received HPV vaccines or who have not received all three doses. The opportunity afforded by HPV vaccines to prevent cancers safely and effectively should not be disregarded. CDC estimates that increasing HPV vaccination rates from current levels to 80 percent would prevent an additional 53,000 future cervical cancer cases among girls who now are 12 years old or younger over the course of their lifetimes. This estimate does not include the thousands of U.S. cases of other HPV-associated cancers that likely also would be prevented within the same timeframe. A growing proportion of these cancers—most notably, oropharyngeal cancers—will occur in males, who currently are vaccinated at very low rates. High rates of HPV vaccination have been achieved in other high-income countries and are achievable in the United States through an integrated effort that includes multiple evidence-based strategies.

The following sections of this report include four goals to increase HPV vaccine uptake. Three goals focus on increasing uptake in the United States (Part 3) and the fourth addresses ways the United States can help increase global uptake of the vaccines (Part 4). Several high-priority research areas also are identified (Part 5).

* Estimates of incidence and mortality of cervical cancer by state are available on the NCI State Cancer Profiles website: http://statecancerprofiles.cancer.gov/cgi-bin/quickprofiles/profile.pl?00&057#deathMap.

Recommendations and some of the stakeholders responsible for implementing them are summarized in Appendix B. The Panel urges all stakeholders—including federal and state governments, healthcare professionals, nongovernment organizations with a focus on public health, and members of the public—to contribute to efforts to achieve this goal and protect millions of men and women around the world from the burden of avoidable cancers and other diseases and conditions in the coming years. Organized, mutually reinforcing efforts could have synergistic impact on HPV vaccine uptake. The Panel views this as an important opportunity to catalyze the prevention of cancer that should not be squandered.


Sometimes,
a mother's care is
HMC



PART 3
ACCELERATING HPV VACCINE UPTAKE IN THE UNITED STATES

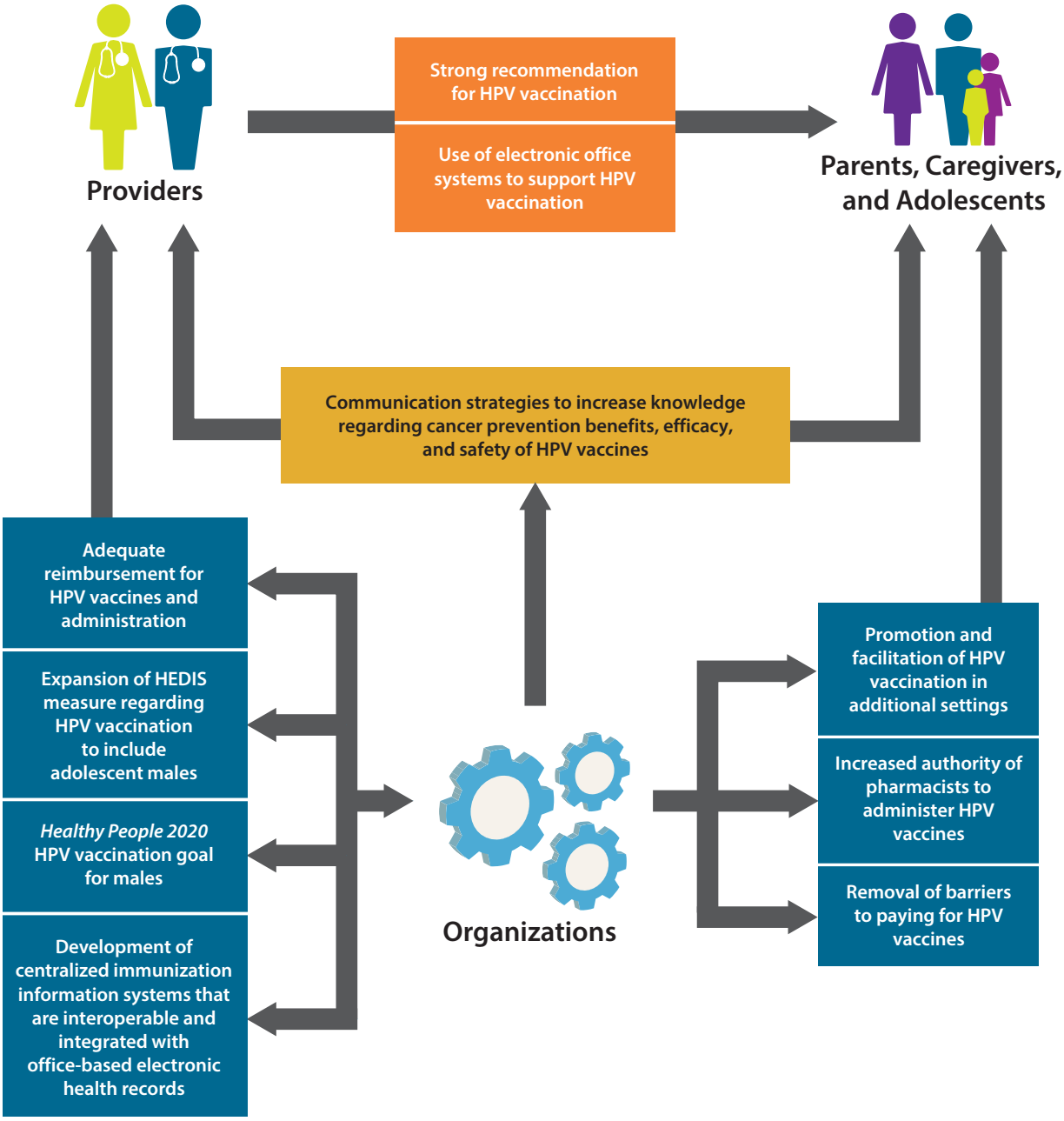
Experiences in some states and several other countries demonstrate that much higher uptake of HPV vaccines is possible. Lessons learned from the introduction of other vaccines and from a large literature on vaccine uptake show that widespread adoption of HPV vaccines is not likely to occur without comprehensive, targeted interventions aimed at providers, parents or other caregivers, and adolescents. The Panel recommends three critical goals that must be achieved to increase uptake of HPV vaccines in the United States, with the ultimate goal being completion of the full three-dose vaccine series by all age-eligible adolescents for whom the vaccine is not contraindicated. Particular attention should be paid to areas with high cervical cancer incidence rates and low HPV vaccine uptake. Figure 6 illustrates some of the audiences and objectives key to achieving these goals.

Goal 1: Reduce Missed Clinical Opportunities to Recommend and Administer HPV Vaccines

According to a recent report from CDC, missed clinical opportunities are the most important reason why the U.S. has not achieved high rates of HPV vaccine uptake.[34] Many vaccine-eligible adolescents do not receive HPV vaccines during visits with their healthcare providers. One survey of parents of 11- to 17-year-old boys and girls found that among those who had not received HPV vaccines, 84 percent of boys and 79 percent of girls had had preventive care visits within the past 12 months.[46] Many times, adolescents received other recommended vaccines at these visits but did not receive HPV vaccines. One report suggests that as many as two-thirds of 11- and 12-year-old vaccine-eligible girls may not be receiving HPV vaccines at visits at which they receive at least one other vaccine.[47]

Several factors contribute to providers' hesitancy in recommending HPV vaccines (see *Factors Contributing to Providers' Hesitancy* on page 15).[48-57] Efforts should be made to address barriers of importance to different kinds of providers. Doing so could substantially reduce

Figure 6
Key Audiences and Objectives for Increasing U.S. HPV Vaccine Uptake



the number of missed opportunities to recommend and administer HPV vaccines. Evidence from other cancer prevention areas, such as avoiding or stopping tobacco use, as well as increasing uptake of other vaccines, indicates that concerted efforts to reduce missed clinical opportunities can change physician behaviors.[8,58-60] There is every reason to believe that those lessons are relevant to HPV vaccination. However, substantial changes in healthcare rarely occur because of minor modifications in one or two facets of systems. Lessons from the past few decades of provider interventions demonstrate that multiple kinds of interventions usually are needed.

Objective 1.1: CDC should develop, test, disseminate, and evaluate the impact of integrated, comprehensive communication strategies for physicians and other relevant health professionals.

Physicians and other healthcare providers should be knowledgeable about HPV infections and associated diseases, protection conferred by HPV vaccines, and safety of these vaccines. They also need tools and strategies to help them communicate with parents and other caregivers about a topic that makes some providers uncomfortable. A multipronged, comprehensive communications strategy is essential to accomplish this. CDC is the logical choice to lead this effort but will require additional funding to do so. Funding should be allocated for design, implementation, and evaluation of sustained communications efforts.

Factors Contributing to Providers' Hesitancy

- Limited understanding of HPV-associated diseases and benefits of HPV vaccination, particularly for males
- Concerns about safety
- Concerns about inadequate reimbursement for vaccines
- Personal attitudes and beliefs
- Discomfort talking to parents and adolescents about a topic related to sexual behavior
- Concerns about parental resistance
- Preference for vaccinating older versus younger adolescents
- Lack of time or incentives to educate parents and patients about HPV and HPV vaccines
- Lack of systems to remind providers to offer vaccines to age-eligible patients

Strategies should be based on evidence and communications best practices.[61] Messages should:

- Focus on HPV vaccines as a tool to prevent multiple cancers.
- Emphasize the importance of vaccinating both males and females.
- Emphasize the importance of vaccinating the primary target age group (11- to 12-year-olds).
- Promote catch-up vaccination for older adolescents and young adults, as needed.*
- Reinforce HPV vaccine efficacy and safety.
- Encourage administration of HPV vaccines as part of an adolescent vaccine platform. Unless contraindicated, HPV vaccines should be administered at the same time as other adolescent vaccines.

The many other stakeholders in the HPV vaccine arena also should collaborate to increase provider understanding and acceptance of HPV vaccines. Mutually reinforcing messages from key organizations will contribute to greater impact than if organizations continue to communicate their individual, nuanced messages. Professional societies and other organizations also should advocate strongly for HPV vaccine use and support their members in increasing uptake.

Objective 1.2: Providers should strongly encourage HPV vaccination of age-eligible males and females whenever other vaccines are administered.

High coverage rates for other adolescent vaccines (Figure 4) make it clear that widespread HPV vaccination is possible in the United States. Nearly 85 percent of adolescents received Tdap vaccines in 2012, but only about half of girls and 20 percent of boys received their first HPV vaccine doses.[13] Adolescents *are* being vaccinated, but all too often *they are not being vaccinated against HPV*.

The Panel cannot overemphasize the role of providers in overcoming disparities in uptake between HPV and other adolescent vaccines. Physicians' recommendation for HPV vaccines to parents and other caregivers is the strongest predictor of HPV vaccination among adolescents.[62,63] When physicians and other providers recommend HPV vaccination, most parents and adolescents comply.[64] However, surveys of both providers and parents indicate

* The Panel supports the actions of CDC and other federal agencies to focus especially on adolescents ages 11-12 years as the ideal target group for HPV vaccination. However, the catch-up period for adolescents and young adults not previously vaccinated is also an important window for cancer prevention. If failure to vaccinate 11- to 12-year-olds is the first missed opportunity, failure to vaccinate young women ages 13-26 who were not previously vaccinated or did not complete the three-dose series and males ages 13-21 is an additional missed opportunity.

that providers frequently fail to recommend HPV vaccines for age-eligible adolescents.[34,65,66] Each time this occurs, there is a missed opportunity to prevent cancer. A recent CDC analysis indicated that if all missed opportunities* for HPV vaccination had been eliminated between the time the ACIP HPV vaccination recommendation was published in 2007 and 2012, 92.6 percent of 13- to 17-year-old U.S. girls would have received at least their first HPV vaccine dose in or before 2012.[34] The Panel recommends in the strongest possible terms that physicians administer HPV vaccines along with other recommended vaccines. This strategy will reduce physicians' and parents' discomfort. Moreover, it will place HPV vaccines where they should be—as essential parts of the adolescent vaccine platform.

92.6% of 13- to 17-year-old U.S. girls would have received at least their first HPV vaccine dose by 2012 if all missed opportunities for HPV vaccination had been eliminated.

Objective 1.3: Healthcare organizations and practices should use electronic office systems, including electronic health records (EHRs) and immunization information systems (IIS), to avoid missed opportunities for HPV vaccination.

Physician surveys indicate that lack of standard office procedures may contribute to low rates of HPV vaccine recommendation and uptake.[48,67] Use of provider reminders improves vaccination coverage in children, adolescents, and adults.[68] Many techniques are useful for delivering reminders (e.g., notes prepared in advance and posted in client charts). The increasing presence of technology in clinical settings offers new tools to reduce missed opportunities for HPV vaccination.

Electronic health record use has increased dramatically among physicians, other providers, and hospitals over the past few years, driven in large part by incentives created by the American Recovery and Reinvestment Act of 2009 (ARRA, P.L. 111-5). As of April 2013, more than half of eligible health professionals (mostly physicians) and 80 percent of eligible hospitals had demonstrated meaningful use of EHRs, up from 17 and 9 percent, respectively, in 2008.[69] Reminders for initiation and completion of HPV vaccine series should be integrated into EHR systems. These reminders will ensure that providers recommend the vaccine to patients during office visits and facilitate follow-up for subsequent doses.

"Meaningful use" refers to the set of standards defined by the Centers for Medicare and Medicaid Services Incentive Programs that allows eligible providers and hospitals to earn incentive payments by meeting specific criteria.

Expanded EHR use also may facilitate delivery of reminders to parents (including those delivered via mobile devices, email, text messaging, and other technologies) informing them that their children are due or overdue for an HPV vaccine dose. Like provider reminders, patient reminder and recall systems are effective for increasing vaccination rates.[70,71] However, reminder and recall systems are underused by pediatricians and other providers.[72,73] Robust centralized immunization information systems that are interoperable and integrated with office-based EHRs could make it easier to implement reminders/recalls. In addition to supporting clinical practice, IIS enable vaccine uptake monitoring and can facilitate study of vaccination impact (see *Health Information Technology and HPV Vaccination* on page 17).

Objective 1.4: Healthcare payers should reimburse providers adequately for HPV vaccines and for vaccine administration and services.

In the U.S., vaccines are financed differently depending upon whether they are covered by public or private funds.[11] Vaccines provided through the Vaccines for Children (VFC) program (see sidebar below) are purchased by the federal government and distributed to VFC providers at no cost.[74] In contrast, providers who serve privately insured patients assume up-front costs for purchasing and maintaining inventories of vaccines and are not reimbursed until vaccines are administered to patients. These costs

Vaccines for Children Program

VFC is a federal entitlement program that provides immunizations at little or no cost to children who might not be vaccinated because of inability to pay. Children younger than 19 years of age are eligible for VFC if they are Medicaid-eligible, American Indian or Alaska Native, uninsured, and/or their insurance does not cover recommended vaccines.

In 2010, an estimated 82 million VFC vaccine doses were administered to approximately 40 million children.

Sources: U.S. Department of Health and Human Services Office of the Inspector General. Vaccines for Children program: vulnerabilities in vaccine management. Washington (DC): DHHS; 2012 Jun. Available from: http://oig.hhs.gov/oei/reports/oei-04-10-00430.pdf

* For this analysis, a missed opportunity was defined as a healthcare encounter occurring on or after a girl's 11th birthday and on or after March 23, 2007 (publication date of ACIP's initial recommendation for HPV vaccination of girls) during which a girl received at least one vaccine but did not receive the HPV vaccine.

can be considerable, particularly for HPV vaccines, which are the most expensive vaccination series universally recommended by ACIP.[75]

Costs for vaccine administration are reimbursed separately. In the case of VFC-provided vaccines, administration costs are reimbursed through Medicaid or paid by patients/parents. For privately insured patients, administration costs are reimbursed by insurance companies.

Up-front costs of purchasing HPV vaccines have been cited as a significant barrier to HPV vaccination in numerous provider surveys.[48-50,66,76-78] In some cases, concerns about cost may lead practices to decide not to stock HPV vaccines.[76,77] Inadequate reimbursement for vaccine administration costs also creates disincentives for strong provider recommendations for HPV vaccination. Reimbursement for vaccine administration by private insurers varies widely and often does not cover provider costs, particularly if only one vaccine is given during a visit.[11,79] This is another reason why integrating HPV vaccines into the adolescent platform is appropriate.

Low levels of reimbursement for vaccine administration by Medicaid (including for vaccines administered through VFC) have been an area of

Health Information Technology and HPV Vaccination

Health information technology (IT) is playing an increasingly important role in healthcare delivery and research. The Health Information Technology for Economic and Clinical Health (HITECH) Act, enacted as part of the American Recovery and Reinvestment Act of 2009, included $19 billion for promotion of health information technology adoption in the United States. Increased use of health IT, driven in part by this investment, has important implications for public health.

Of particular importance to HPV vaccination efforts are improvements in immunization information systems (IIS). IIS are confidential, computerized, population-based systems that collect and consolidate vaccination data within a geographic area (often a state). IIS data can be used to help ensure that individuals receive recommended vaccines (e.g., through use of reminder/recall systems), but also can support vaccination program planning and research. In the U.S., 84 percent of children under 6 years old are included in IIS, but coverage of adolescents is only 53 percent. It should be noted, however, that some state IIS have achieved over 95 percent coverage of both age groups. Efforts to increase IIS coverage of adolescents should be maintained and increased to enable monitoring and improvement of HPV vaccination.

The keys to optimizing the return on investment in health IT are interoperability and integration. Linkages between EHRs, IIS, and other systems would provide unprecedented opportunity for population-based monitoring and research. In the case of HPV vaccines, linkages among IIS and screening or cancer registries would enable study of the impact of HPV vaccination, including differences in rates of HPV-associated precancers and cancers between vaccinated and unvaccinated individuals. Among other things, this information could be used to inform modification of cancer screening guidelines.

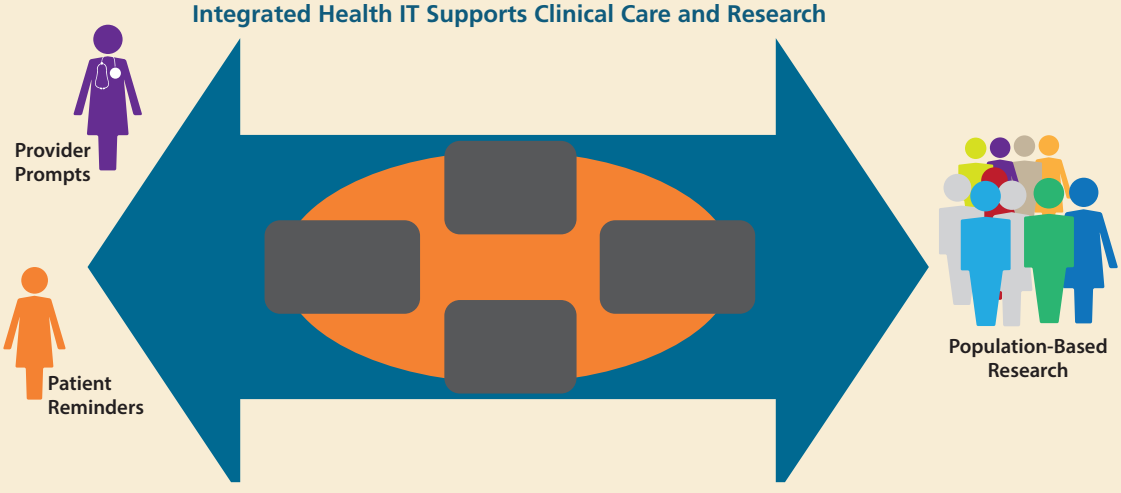
Highly integrated systems are possible, but their development requires cooperation of many stakeholders and significant investment of time and resources. Such cooperation and investment should be encouraged. In instances where system linkages have been achieved, important information already is being generated. For example, the continuum of cervical cancer prevention is monitored in New Mexico through linkage of a population-based cervical cancer screening registry (the only one of its kind in the United States) and HPV vaccine administrative data. These data will be used to inform integration of cervical cancer screening and HPV vaccination.

Sources:

Community Preventive Services Task Force. The Guide to Community Preventive Services. Increasing appropriate vaccination: immunization information systems [Internet]. Atlanta (GA): the Task Force; 2011 Apr 18 [cited 2013 Aug 17]. Available from: http://www.thecommunityguide.org/vaccines/RRimminfosystems.html

Centers for Disease Control and Prevention. Immunization information systems (IIS): 2011 IISAR data participation rates [Internet]. Atlanta (GA): CDC; [updated 2013 Apr 11; cited 2013 Aug 23]. Available from: http://www.cdc.gov/vaccines/programs/iis/annual-report-IISAR/2011-data.html#child

University of New Mexico School of Medicine. NMHPVPR: the New Mexico HPV Pap Registry [Internet]. Albuquerque (NM): UNM; [cited 2013 Aug 20]. Available from: http://hpvprevention.unm.edu/NMHPVPR/



concern for several years.[11] The Affordable Care Act (P.L. 111-148) increased reimbursement for vaccines administered through Medicaid for the first time in nearly 20 years.[80,81] This change, which applies to 2013 and 2014, is laudable and should be extended. The Panel encourages modification of federal laws and regulations as necessary to ensure adequate Medicaid reimbursement for vaccine administration in 2015 and beyond.

Inadequate provider reimbursement creates disincentives for strong HPV vaccination recommendations.

Continued monitoring is needed to ensure that vaccine financing issues do not limit access to HPV or other vaccines. At a minimum, payers should reimburse direct and indirect costs associated with purchasing and maintaining inventories of recommended vaccines.[82] Also, reimbursement for vaccine administration by private payers and Medicaid should be at least equal to reimbursement provided through Medicare.

Objective 1.5: The current Healthcare Effectiveness Data and Information Set (HEDIS) quality measure for HPV vaccination of adolescent females should be expanded to include males.

HEDIS is a set of standardized measures related to healthcare and services.[83] More than 90 percent of U.S. health plans use HEDIS to measure performance. Accreditation by the National Committee for Quality Assurance (NCQA) depends in large part on how well health plans perform with respect to these measures. In addition, health plan purchasers often use HEDIS data when selecting plans. Plans have an incentive to change practices and make improvements to optimize their HEDIS scores.

In 2012, a HEDIS measure was created to assess the percentage of female adolescents 13 years of age who had had three doses of HPV vaccine by their thirteenth birthdays.[84] After two years of testing, the measure recently was approved by the NCQA Committee on Performance and will be included as a publicly reported HEDIS measure in 2014.[85] The Panel commends adoption of this measure. It likely will promote HPV vaccine uptake among girls. However, it does not address vaccination of boys, who also are at risk of HPV-associated diseases, including cancer. NCQA should expand the HEDIS measure on HPV vaccination to include adolescent boys.

Objective 1.6: Create a *Healthy People 2020* HPV vaccination goal for males.

Current *Healthy People 2020* objectives include increasing HPV vaccine completion rates for females ages 13 to 15 years to 80 percent.[5] *Healthy People 2020* objectives should be updated to include an HPV vaccination goal for males equivalent to that for females. This is consistent with ACIP's 2011 recommendation for HPV vaccination of adolescent males.

The *Healthy People* initiative provides science-based, 10-year national objectives for improving the health of the U.S. population. These objectives are used by federal, state, and local health and public health programs and others to inform prioritization and planning processes.

Goal 2: Increase Parents', Caregivers', and Adolescents' Acceptance of HPV Vaccines

Parents' and other caregivers' knowledge, attitudes, and beliefs affect whether their children receive vaccines, including HPV vaccines. Most parents believe that vaccines protect their children from potentially life-threatening diseases, but some refuse one or more recommended vaccines based on concerns about safety and other factors.[86] One study found that parents were more likely to refuse HPV vaccines than other recommended vaccines.[86] Research has identified several reasons parents do not vaccinate their adolescents against HPV (see *Reasons Parents Did Not Intend to Vaccinate Their Adolescents Against HPV*).[34,57,65]

These reasons demonstrate both the failure of providers to recommend HPV vaccines strongly and

Reasons Parents Did Not Intend to Vaccinate Their Adolescents Against HPV

- Vaccination not needed, particularly for males
- Vaccination not recommended by healthcare provider
- Safety concerns
- Lack of knowledge about the vaccines or diseases caused by HPV infections
- Son or daughter not sexually active
- Son or daughter too young to be vaccinated against HPV
- Cost of vaccines

parental lack of understanding about HPV vaccines and their safety profiles, especially for males.

Other studies have provided additional insight into parents' views. Surveyed pediatricians and family practice physicians reported that parents of young adolescents sometimes are upset by recommendations that their children receive vaccines against sexually transmitted infections. Providers also report more vaccine refusals among parents of younger versus older adolescents.[50] This trend is troubling in light of the fact that the vaccines are most effective when administered before initiation of sexual activity, and sexual debut for some adolescents may occur earlier than their parents expect.[24,25,87] Some parents have expressed concern that HPV vaccination would encourage sexual activity, although this does not appear to be a major barrier to HPV vaccination uptake. To date, studies have not shown a relationship between receipt of HPV vaccines and initiation of sexual activity[88-90] or sexual activity-related outcomes (e.g., pregnancy, sexually transmitted infection testing or diagnosis, contraceptive counseling).[91] One study noted a higher number of lifetime partners among sexually active girls who had received HPV vaccines compared with unvaccinated sexually active girls.[29] However, the correlation does not mean that HPV vaccines caused these adolescents to have more sexual partners. It is equally plausible that the physicians and/or parents of these adolescents anticipated their greater level of sexual activity and were more likely to encourage HPV vaccination for them than for girls who they viewed as less likely to have multiple sexual partners.

Objective 2.1: CDC should develop, test, and collaborate with partner organizations to deploy integrated, comprehensive communication strategies directed at parents and other caregivers, and also at adolescents.

CDC is a logical choice to lead development and implementation of communications strategies for parents and other caregivers, as well as adolescents. Other stakeholder groups also should provide accurate information to parents and caregivers. Research has indicated that parents and adolescents may distrust information from pharmaceutical companies.[92,93] This is one reason it is important that communications come from impartial sources.

Communication strategies—including messages and modes of delivery—should incorporate lessons from qualitative and quantitative research and also should be sensitive to cultural, literacy/health literacy, and language differences of target populations. While recognizing that all messages should be tested through research, the following points should be considered as part of communications strategies:

- Frame HPV vaccines as vaccines that prevent cancers.
- Provide factual information about which adolescents should be vaccinated (routine vaccination of 11- to 12-year-olds, with catch-up vaccination of older adolescents and young adults), along with how-to information (e.g., which providers can administer vaccinations, where vaccines are available in different communities).
- Address common myths, misconceptions, and misinformation about HPV vaccines.
- Highlight the safety of HPV vaccines.
- Emphasize the importance of vaccinating both males and females as part of the adolescent vaccine platform.
- Address both initiation and completion of the HPV vaccine series.
- Aim to resonate emotionally with parents, other caregivers, and adolescents.

HPV vaccines should be framed as vaccines that prevent cancers.

The ways in which messages are delivered are important.[61] Modes of communication should be informed by research and tested with target audiences, but could include:

- Websites, blogs, social media, and print and electronic media (e.g., mobile phones and text messages) accessible by and acceptable to parents.
- Recruitment of vaccination champions who are influential for particular target audiences.
- Development of companion communication tools for use with parents/caregivers and adolescents in healthcare providers' offices (e.g., posters, brochures, computer kiosks). Such tools may make it easier for physicians to convey strong recommendations regarding HPV vaccination.

Goal 3: Maximize Access to HPV Vaccination Services

Several characteristics of service delivery affect vaccine initiation and completion. Vaccines should be available where adolescents receive healthcare. It should be convenient to initiate and complete the HPV vaccine series, and cost should not be a barrier. The Panel encourages adoption of the National Vaccine Advisory Committee Standards for Adult Immunization Practices as a critical component of quality vaccine delivery and administration.[94]

The American Academy of Pediatrics[95] and American Academy of Family Physicians[1] prefer that all adolescents receive primary care, including vaccinations, within a medical home (see sidebar).[96] Medical homes are the optimal environment for administration of HPV vaccines, particularly the first dose, because they provide opportunities to educate parents and adolescents and to deliver other important preventive care services. Reducing missed clinical opportunities for HPV vaccination in physicians' offices and other medical practices will go a long way toward increasing HPV vaccine uptake. However, the Panel recognizes that providing additional venue choices may increase the likelihood that adolescents will receive all three HPV doses. **As such, the Panel recommends increasing the range of venues and providers for HPV vaccination. In this way, HPV vaccination would occur within the "medical neighborhood," in venues outside of but in coordination with the medical home**. The discussion below focuses especially on pharmacies and raises some issues related to schools.

The Patient-Centered Medical Home is a care delivery model whereby patients' treatments are coordinated through their primary care physicians to ensure that patients receive necessary and appropriate care when and where they need it, in a manner they can understand.

Source: American College of Physicians.

Objective 3.1: Promote and facilitate HPV vaccination in venues outside the medical home.*

While medical homes are the optimal environment for delivery of preventive health services, including vaccinations, many adolescents—particularly males, racial/ethnic minorities, adolescents from low-income families, and older adolescents—do not receive regular preventive care through medical homes.[97-102] Lack of a medical home may affect immunization coverage for all vaccines, but HPV vaccination is likely disproportionately affected, given the number of visits needed to complete the series.[102]

Many adolescents do not receive regular preventive care through medical homes.

The range of settings in which HPV vaccines may be administered to adolescents should increase. HPV vaccines should be available to adolescents in places where they interact with healthcare providers. Schools and pharmacies are two promising alternative settings for HPV vaccination in the United States.[102] Other settings may include health department clinics, urgent care centers, and emergency rooms. Survey results indicate that accessing HPV vaccines in alternative settings appealed to adolescent boys who had not had recent healthcare visits, as well as to their parents.[103,104] Given low vaccination rates among adolescent boys, strategies should be undertaken to reach this population more effectively.

Schools can educate adolescents and parents about the importance of vaccination and provide venues for vaccine administration. School-based programs have been extremely effective in other high-income countries, such as Australia, the United Kingdom, and Canada.[105-107] In the United States, school-based programs face challenges not encountered in these other countries. For example, decisions about whether to offer school-located vaccination in the U.S. generally are made by local superintendents and school boards. In addition, student populations often are covered by multiple healthcare payers, creating billing and reimbursement challenges. All of these factors point to the complexity of implementation and are the reasons why the Panel, which initially was inclined to recommend school-located vaccination programs, concluded that other approaches are more likely to be effective in the U.S., especially in the face of recent data regarding missed clinical opportunities.[34] Nevertheless, school-located vaccination programs may be feasible and effective for some populations in some settings (e.g., schools in which a large percentage of students are VFC- or Medicaid-eligible). **Ongoing efforts to implement school-located programs (e.g., Health4Chicago program[108]) should be monitored and expanded, as appropriate. Furthermore, if vaccination rates in the U.S. do not**

* In alignment with National Vaccine Advisory Committee recommendations, "venues outside the medical home" refer to settings complementary to the medical home that are shown to be appropriate and effective.

improve dramatically over the next several years, the feasibility of school-located vaccination should be reexamined.

Pharmacies are another venue that could be utilized to increase HPV vaccination rates. Pharmacies are highly accessible to most people in the United States; about 275,000 licensed pharmacists practice in nearly 60,000 pharmacies across the country.[109,110] In health professional shortage and rural areas, pharmacists often are the most prevalent healthcare providers.[111] Other advantages of pharmacies include extended hours of operation (often including weekends) and availability of services without appointments. Pharmacists have played an important role in administering seasonal influenza and other vaccines in the United States. During the 2011-2012 flu season, 20 percent of U.S. adults who received flu vaccines received them in pharmacies.[112] Adolescents and their parents are open to having pharmacists provide adolescent vaccinations, including HPV vaccines.[103,104] Pharmacies also may be a place to reach young adults for catch-up vaccinations. However, in many states, pharmacists' authority to administer HPV vaccines is limited, precluding them from playing an active role in increasing HPV vaccination among primary target populations.

Objective 3.2: States should enact laws and implement policies that allow pharmacists to administer vaccines to adolescents, including younger adolescents.

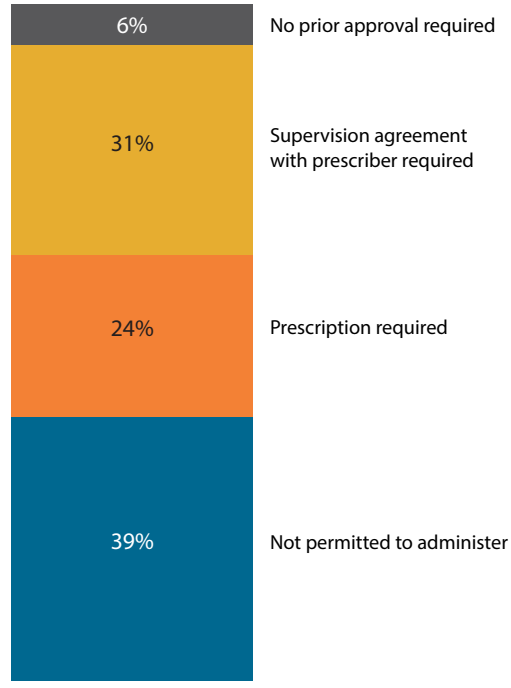
Pharmacists' authority to provide HPV vaccines to adolescents varies widely by state. A 2012 survey[113] of representatives of state pharmacy organizations in all 50 states and the District of Columbia found that pharmacists in more than one-third of states were not permitted to administer HPV vaccines to 12-year-old girls (Figure 7), though many of these states did allow pharmacists to provide the vaccine to women ages 19 and older. In states where pharmacists were allowed to administer the vaccine, mechanisms were highly variable. In the most permissive states, pharmacists could administer HPV vaccines to 12-year-old girls without prior approval from a prescriber,* while in other states pharmacists were required to sign supervision agreements with a specific prescriber or could vaccinate only individuals with a prescription.

States should adopt policies that allow pharmacists to deliver HPV vaccines to primary target populations (11- and 12-year-old boys and girls and others completing the three-dose series). Policies should be permissive enough to facilitate access to vaccination.

Objective 3.3: Overcome remaining barriers to paying for HPV vaccines, including payment for vaccines provided outside the medical home and by out-of-network or nonphysician providers.

While HPV vaccines are among the most expensive in the United States (about $400 for the three-dose series),[114] their cost is covered for most age-eligible adolescents through private health insurance or public programs. Under provisions of the Affordable Care Act, all new group and individual health plans established or significantly changed since March 23, 2010, are required to cover HPV vaccination for both girls and boys without cost to patients.[115,116]** HPV vaccines also are available through VFC at no cost for eligible children under age 19 (there may be some cost for vaccine administration for children not

Figure 7
Authority of Pharmacists to Administer HPV Vaccines to 12-Year-Old Girls in 2012



Source: Brewer NT, Chung JK, Baker HM, Rothholz MC, Smith JS. Pharmacist authority to provide HPV vaccine: novel partners in cervical cancer prevention. Gynecol Oncol. [Epub 2013 Dec 19]

* In some of these states, a public official permitted use of his or her name on supervision agreements (e.g., standing orders, protocols, collaborative practice agreements).

** So-called grandfathered plans that were in place before the Affordable Care Act was implemented are not required to cover HPV vaccination. Plans lose this exempted status if they make significant changes in cost sharing, benefits, employer contributions, or access to coverage. In 2013, 36% of people who get health insurance through their jobs are enrolled in grandfathered plans. This is down from 48% in 2012 and 56% in 2011, and the number is expected to continue to decline as plans lose grandfathered status. Source: Kaiser Family Foundation and Health Research & Educational Trust. Employer health benefits: 2013 annual survey. Menlo Park (CA): KFF; 2013 Aug. Available from: http://kff.org/private-insurance/report/2013-employer-health-benefits/

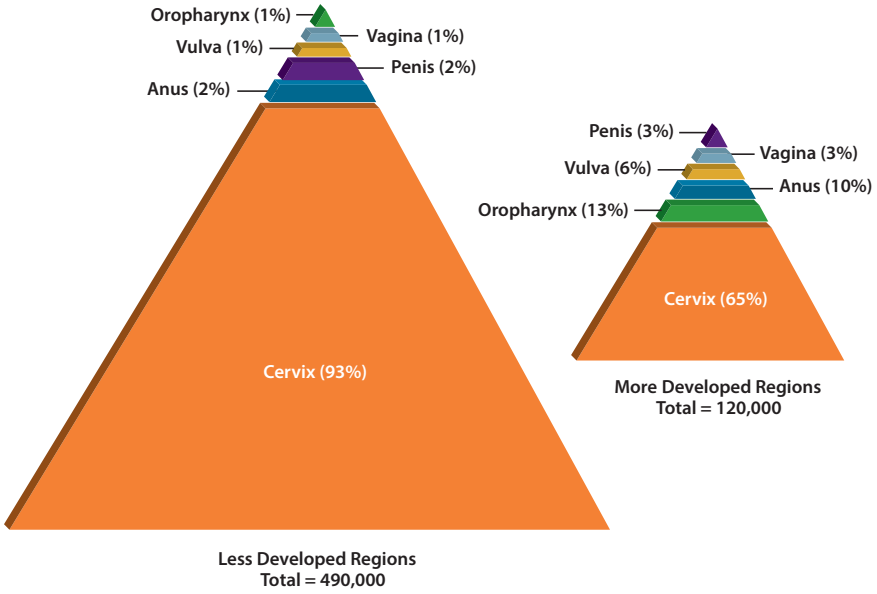
covered by Medicaid).[74] Medicaid covers HPV vaccines for males and females 19 and 20 years of age through the Early and Periodic Screening, Diagnostic, and Treatment benefit.[117] Cost of HPV vaccines may be a barrier for uninsured young adults and for adolescents covered by older health plans not required to adhere to the law's requirements for vaccine coverage. These barriers should be addressed, although they are not the main reason for lagging HPV uptake.

Additional financial barriers may come into play, particularly for privately insured patients, if HPV vaccination becomes available in complementary settings and/or from additional provider types. The Affordable Care Act requires health insurers to cover all ACIP-recommended vaccinations at no cost to consumers when provided by in-network providers, which increases access of insured adolescents to HPV vaccines and other important preventive health services.[116] Cost may be a barrier, however, if privately insured adolescents obtain care from providers outside their networks. Patients covered by public programs (e.g., VFC, Medicaid) also must receive vaccines from recognized providers, although any provider authorized to prescribe vaccines under state law can become a VFC provider.[74] Pharmacists also can become VFC providers if granted authority to administer vaccines under state law.[118,119] These potential barriers should be addressed to ensure that they do not interfere with HPV vaccine uptake.

PART 4
INCREASING GLOBAL HPV VACCINATION

The burden of HPV-associated cancers extends beyond the borders of the United States, affecting populations in every country. Patterns of HPV-associated cancers differ by region. Cervical cancer is the most common HPV-associated cancer globally. In the United States and other more developed regions, other sites account for a significant proportion of HPV-associated cancers (Figure 8). In contrast, in less developed regions, more than 90 percent of HPV-attributed cancers are cervical cancers.[12]

Figure 8
Numbers of HPV-Associated Cancers in Less Developed and More Developed Regions*



Note: Global estimates of genital warts and RRP incidence are not available.
Source: de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol. 2012;13(6):607-15.

Figure 9 illustrates the uneven burden of cervical cancer across the world, with mortality rates in some parts of Africa being 15 times higher than in North America.[120] These disparities stem, in part, from the fact that the United States and other high-income countries have widespread cervical cancer screening programs and treat precursor lesions and early invasive cervical cancers, dramatically reducing the numbers of new cases and deaths. The absence of such services in many lower-income, less developed countries has resulted in cervical cancer being a leading cause of cancer-related death among women.[120] While the prevalence of HPV infections and distribution of HPV types vary by region, research has found consistently that HPV16 and HPV18, the cancer-causing strains that HPV vaccines protect against, are responsible for at least two-thirds of cervical cancer cases in populations around the world.[121,122] This fact provides a strong indication that HPV vaccines will be effective virtually everywhere. Delaying implementation of HPV vaccine programs will result in missed opportunities to prevent HPV infections responsible for more than 400,000 cancers each year.

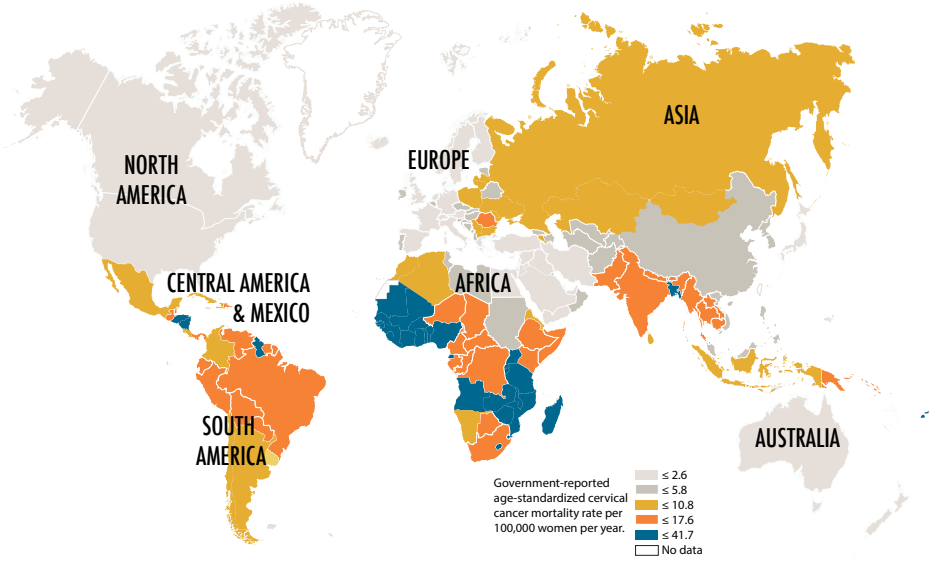
As with cervical cancer screening programs, HPV vaccination programs have been implemented primarily in high-resource areas. Australia, the United Kingdom, and parts of Canada have launched highly effective programs that have achieved higher HPV vaccine uptake than the United States (Figure 10).[34,106,107,123] Australia, the U.K., and Canada have national healthcare programs that differ significantly from the healthcare delivery system in the United States, which includes many payers. Nonetheless, the U.S. can learn from successful HPV vaccination programs in other countries, which, in some cases, already have led to measurable public health benefits.[30,31]

Addressing the global burden of HPV-associated cancers requires implementation of HPV vaccination programs in low- and middle-income countries (LMICs), where the majority of HPV-associated cancer cases occur. LMICs face a number of barriers, including limited financial resources, inadequate healthcare delivery systems, and, in some instances, expertise gaps in program planning and implementation.[124] The United States should collaborate with global organizations and LMICs to support efforts to plan and implement HPV vaccination programs in these countries. Learning should be bidirectional; the U.S. can learn from what is accomplished in other countries.

Efforts to introduce and expand HPV vaccination in LMICs are gaining momentum through efforts of

* The terms "developing countries," "developing world," "developing economies," and "low- and middle (or medium)-income countries (LMICs)" are not entirely synonymous, and definitions vary among international aid agencies. The same is true of the terms "developed countries," "developed world," "developed economies," and "higher-income countries (HICs)." However, many agencies use these terms interchangeably except when describing gradations of overall development that may reflect not only Gross National Income (GNI) but also assessments of sustainable infrastructure, human asset indices (e.g., literacy, nutrition), and economic and environmental vulnerabilities. Thus, countries grouped by income level may have significantly varied levels of development. These differences are important because they may determine countries' eligibility for specific types of assistance.

Figure 9
Global Cervical Cancer Mortality Rates

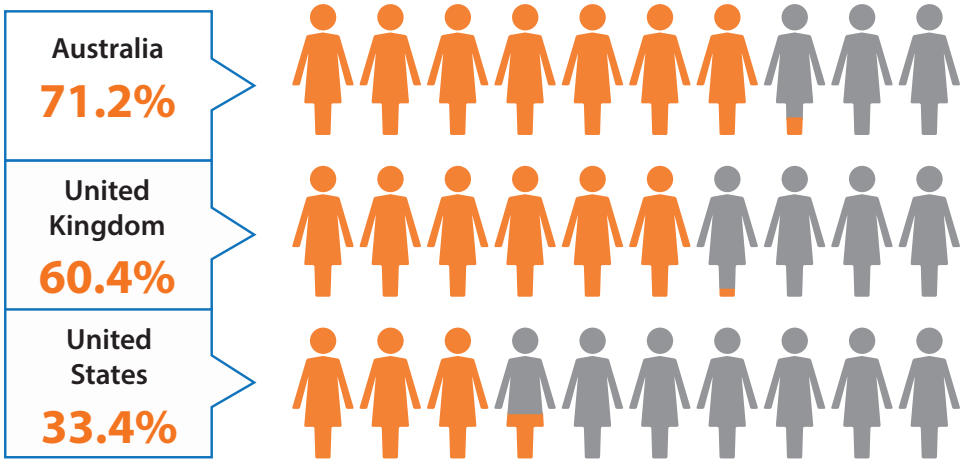


Modified from: Crow, JM. HPV: the global burden. Nature. 2012;488:S2-3. Data from: World Health Organization, Institut Catala d'Oncologia. Human papillomavirus and related cancers: summary report update. Barcelona (ES): WHO/ICO; 2010 Nov 15.

the GAVI Alliance (formerly the Global Alliance for Vaccines and Immunisation) and the Pan American Health Organization (PAHO) Revolving Fund. The GAVI Alliance is a public-private partnership focused on increasing access to immunization in poor countries. In 2013, GAVI launched a demonstration program that will provide HPV vaccines to more than 180,000 girls in eight countries.[125] The demonstration programs are designed to give each country the opportunity to test its ability to establish systems needed to implement a national HPV vaccination program (e.g., medical staff, supplies, distribution systems, supply management). GAVI also is supporting implementation of a nationwide HPV vaccination program in Rwanda and partnering with the Islamic Development Bank (IDB) to accelerate the introduction of life-saving vaccines, including HPV, in IDB member countries.[126,127]

In June 2013, GAVI announced successful negotiation for a sustainable supply of HPV vaccine for use in

Figure 10
HPV Vaccine Three-Dose Coverage Among Girls in High-Income Countries



Note: National data on HPV vaccine coverage in Canada are not available. However, Canadian provinces report three-dose coverage among target age groups between 50 and 85 percent.
Sources: Australia (girls turning 15 in 2011): Australian Government Department of Health and Ageing. Human papillomavirus (HPV) [Internet]. Woden (AU): the Department; [updated 2013 Feb 14; cited 2013 Aug 16]. Available from: http://www.health.gov.au/internet/immunise/publishing.nsf/Content/immunise-hpv; United Kingdom (12- to 19-year-old girls): Sheridan A, White J. Annual HPV vaccine coverage in England in 2009/2010. London (UK): Health Protection Agency, UK; 2010 Dec 22. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/215800/dh_123826.pdf; United States (13- to 17-year-old girls): Centers for Disease Control and Prevention. Human papillomavirus vaccination coverage among adolescent girls, 2007-2012, and postlicensure vaccine safety monitoring, 2006-2013—United States. MMWR. 2013;62(29):591-5; Canada: Saraiya M, Steben M, Watson M, Markowitz L. Evolution of cervical cancer screening and prevention in United States and Canada: implications for public health practitioners and clinicians. Prev Med. 2013;57(5):426-33.

developing countries at an unprecedented low price of $4.50 per dose for Gardasil® and $4.60 per dose for Cervarix®.[125] The lowest previous public-sector cost was $13 per dose. The goal is that by 2020, 30 million girls in 40 countries get the vaccines at or below these prices.

The PAHO Revolving Fund provides a mechanism for many GAVI-ineligible, middle-income nations in Latin America and the Caribbean to procure HPV vaccines at reduced prices.[128] Revolving Fund Member States pool their resources to purchase vaccines and related supplies at discounted bulk rates. The fund also provides countries a 60-day line of credit for purchases and assists with the logistics of vaccine procurement. As of 2012, four countries had introduced HPV vaccines with PAHO Revolving Fund support.[129]

Goal 4: Promote Global HPV Vaccine Uptake

Objective 4.1: The United States should continue its collaboration with and support of GAVI to facilitate HPV vaccine introduction and uptake in low-income countries.

Numerous countries and organizations, including the United States, support GAVI. In 2013, direct support for GAVI from the U.S. government totaled $145 million in donations and pledges.[130] This investment in global HPV-associated cancer control via funding of GAVI is appropriate. Additional support should be provided as necessary and appropriate to scale up implementation of HPV vaccination programs. Implementation science principles should be brought to bear in this process (e.g., paying close attention to processes of implementation to understand what works and what does not work). Best practices should be shared.

Some middle-income countries are not eligible for GAVI funding, yet have a great need for assistance to develop and implement national vaccine programs. Other mechanisms will be required to help these nations bring HPV-associated cancer prevention to their populations.

Objective 4.2: The United States should continue to support global efforts to develop comprehensive cancer control plans and cancer registries in low- and middle-income countries.

Limited public health and healthcare infrastructure creates challenges for implementing HPV vaccination programs in many LMICs. The World Health Organization (WHO) plays a central role in promoting public health in LMICs. The United States partners with WHO on many key initiatives and also independently supports capacity building in several LMICs.

U.S. government agencies have provided extensive support to WHO efforts to increase HPV vaccination around the world. CDC and NCI have provided technical expertise to support WHO in developing policies and recommendations related to HPV vaccination since 2006. CDC participated in creating WHO position papers and provided assistance and guidance to WHO and countries with vaccine introduction, communications, monitoring, and evaluation. In addition, the CDC HPV laboratory worked with the WHO HPV LabNet to improve standardization of laboratory procedures. CDC also has secondees* focused on new vaccine introduction, including HPV vaccines, at WHO headquarters and other WHO offices. Activities conducted by CDC staff and secondees include providing technical assistance to countries for vaccine introduction, vaccine impact monitoring, postintroduction evaluations, and coverage surveys to evaluate vaccine programs.

In 2013, WHO released a Global Action Plan for Prevention and Control of Noncommunicable Diseases (NCDs) aimed at reducing mortality from several NCDs, including cancers.** The WHO global monitoring framework includes several targets and indicators related to prevention and control of cancers. These include decreasing premature mortality due to cancer by 25 percent by 2025, improving HPV vaccine coverage, monitoring cancer incidence, and increasing the proportion of women who are screened for cervical cancer.[131] Increased attention to cancer on the global stage will provide opportunities for the United States to contribute to cancer prevention and control efforts, including those that facilitate HPV vaccination in the short or long term.

* A person transferred temporarily to alternative employment.

** Noncommunicable diseases are diseases that are not passed from person to person. Although cancer can be caused by HPV or some other infectious agents that are passed from person to person, cancer itself does not spread this way and is thus considered an NCD.

In light of the emerging focus on NCDs, the International Agency for Research on Cancer (IARC) recently launched the Global Initiative for Cancer Registry Development in Low- and Middle-Income Countries (GICR) to improve the capacity of these countries to produce high-quality information on the burden of cancer so that effective cancer control policies can be developed, implemented, and evaluated.[132] Many LMICs do not have population-based cancer registries, making it impossible to accurately determine rates of cervical and other HPV-associated cancers. Panel workshop participants suggested that the absence of information about the burden of HPV-associated cancers and the prevalence of HPV infections within LMICs may make some governments hesitant to invest in HPV vaccination programs.[124] NCI and CDC have joined a number of other organizations from around the world as partners in the GICR initiative and are contributing funding and serving in an advisory capacity.[133]

The United States also engages in global public health activities. For example, CDC supports training in field epidemiology in several LMICs, and NCI and CDC are creating modules related to cancer prevention and control.[134] The NCI Center for Global Health develops and implements plans to inform cancer control efforts and provides technical assistance as countries work to implement cancer control programs.[135] The U.S. Agency for International Development Global Health Initiative helps countries strengthen their health systems, integrate service delivery, and create awareness to generate demand for available services.[136,137] In addition, the U.S. government has partnered with several other organizations to create Pink Ribbon Red Ribbon®, an initiative focused on improving prevention, screening, and treatment for cervical and breast cancers in sub-Saharan Africa and Latin America.[138] This initiative is leveraging the existing platform of the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) to accomplish its goals, including increasing access to HPV vaccination.[139]

The U.S. should continue to work with global partners to facilitate access to and uptake of HPV vaccines. These efforts should include research and capacity-building efforts by CDC and NCI, including the recently created NCI Center for Global Health. In particular, the U.S. should help increase the capacity of LMICs to conduct surveillance and enact robust cancer control programs.

PART 5

HIGH-PRIORITY RESEARCH TO ADVANCE PREVENTION OF HPV-ASSOCIATED CANCERS

HPV vaccines and their public health benefits were enabled by decades of laboratory, clinical, and population-based research. Additional research in several areas could increase the impact of HPV vaccination. These include the potential for a two- or one-dose vaccine and better vaccines, as well as improved ways to communicate about HPV vaccines. Finally, it is not too early to anticipate the time when HPV vaccination is disseminated widely across populations, and to ask how cervical cancer screening guidelines will then need to be changed.

1. Investigate More Convenient Dosing Schedules for Current Vaccines

Recommended dosing regimens for HPV vaccines—three doses over six months—are expensive and create logistical and other difficulties for organizations that purchase and administer them. Confirmation that extended dosing schedules and/or fewer vaccine doses adequately protect against HPV infections would have enormous implications for HPV vaccine programs in both high- and low-resource settings. **Evidence that one or two doses are sufficient to protect against particular HPV infections could be an important factor in increasing HPV vaccine uptake in the U.S. and around the world**.

Extended Dosing Schedule

In the U.S., many adolescents who initiate the HPV vaccine series do not complete it within the recommended six months or at all.[34,140] This is in part because most adolescents do not visit their providers this frequently. The six-month schedule can be even more challenging in low-resource settings with suboptimal healthcare delivery infrastructure. Spreading doses out over one to two years would ease the logistical challenges of HPV vaccine delivery in both high- and low-resource settings. In the U.S., a two-year schedule would mean that adolescents could receive one dose at each of three annual preventive visits. In low-income countries, an extended schedule may provide an opportunity to incorporate HPV vaccination into existing vaccine programs.[141] A study of adolescent girls in Vietnam found similar immune responses to Gardasil® whether the three doses were spread over 6, 9, 12, or 24 months.[141] However, additional research may be needed to determine whether this protection is long-lasting and/or whether similar results will be seen in other populations and with Cervarix®.

Fewer Doses

Increasing evidence suggests that fewer than three HPV vaccine doses may be efficacious. In one clinical trial, women who received only one or two doses of Cervarix® were protected against persistent cervical infections with HPV16 and 18.[142] Antibodies against HPV16 and HPV18 remained stable for up to four years in women who received one dose, suggesting that even a single dose of the vaccine may induce long-term protection.[143] Studies in Canada[144] and Vietnam[141] suggest that Gardasil® also may induce lasting immunity to target HPV types in adolescent girls after only two doses. While these results are promising, additional research is needed to confirm that one- or two-dose protection is long-lasting and occurs in other populations (e.g., other age groups, men).

Evidence that one or two doses of HPV vaccine could prevent cancer would dramatically reduce financial and logistical challenges in the U.S. and around the world.

Insight into the effectiveness of fewer than three doses likely will be gained as adoption of HPV vaccines increases in a variety of settings around the world. Some regions, including parts of Canada,[145,146] have implemented two-dose regimens. In the U.S., NCI and CDC are monitoring results of ongoing clinical trials. It is critical that mechanisms are in place to help FDA reach decisions about dose and schedule as soon as valid data are available. **The Panel recommends strongly that funding agencies place a very high priority on answering critical questions about HPV vaccine dose and scheduling**.

2. Develop Next-Generation Vaccines That Provide Broader Protection and/or Are Easier to Store and Administer

Efforts already are underway to improve the effectiveness of currently available HPV vaccines. A vaccine under development by Merck, V503, is designed to protect against the four HPV types covered by Gardasil® and five additional cancer-causing HPV strains (31, 33, 45, 52, and 58). In a Phase III clinical trial of V503, the vaccine prevented approximately 97 percent of cervical, vaginal, and vulvar precancers caused by these five strains in women who were not infected with these HPV types prior to vaccination. The vaccine also generated immune responses to HPV6, 11, 16, and 18 that were comparable to those generated by Gardasil®.[147] V503 has potential to prevent 90 percent of the world's cervical cancer cases, as well as provide broader protection against other anogenital and oropharyngeal cancers caused by HPV. Other research groups are experimenting with the inclusion of different viral proteins in an effort to achieve broader protection against more HPV types.[148]

Changes in vaccine formulation that would make HPV vaccines easier to administer or store also could increase vaccine coverage. For example, dissemination of the vaccine in low-resource settings would be more feasible if vaccines did not need to be refrigerated.

A noninjected form of the vaccine also would ease delivery.

3. Explain the Natural History of Oropharyngeal HPV Infections

Over the past several decades, research has yielded extensive knowledge about how HPV infections of the cervix progress to invasive cervical cancer.[149] There still is much to be learned about how HPV infections lead to cancer at other sites. Knowledge of the natural history of oropharyngeal HPV infection is particularly weak, in large part because the location of the oropharynx makes it difficult to collect tissue samples for study. Limited knowledge about oropharyngeal precancers creates challenges for testing the efficacy of HPV vaccines in preventing oropharyngeal cancers in clinical trials. There is an urgent need to develop biomarkers or other markers that would provide better ways to understand the natural history of oropharyngeal cancers.[150] Natural history studies of the oropharynx would benefit from technologies that permit noninvasive detection and characterization of lesions.

Limited knowledge about oropharyngeal precancers creates challenges for testing the efficacy of HPV vaccines in preventing oropharyngeal cancers in clinical trials.

4. Develop More Effective Ways to Communicate About HPV-Associated Diseases and HPV Vaccines

HPV vaccines are a safe and effective way to prevent multiple cancers, genital warts, and RPP. Surveys of physicians, parents, and other caregivers indicate a lack of understanding about HPV-associated diseases and the safety, efficacy, and need for HPV vaccines.[34,48-54,65] Communication and behavioral research are needed to determine the best ways to convey messages to important stakeholders involved in decisions about HPV vaccination. This includes research using mobile health interventions and behavioral economics approaches. Specific strategies and messages should be tested and optimized for different populations, with consideration of sociocultural factors, specific barriers experienced by particular populations, numeracy, and health literacy. Research should focus on both initiation and completion of the vaccine series.

Research also should inform development of tools that can be used by providers to facilitate communication with parents and adolescents. The process by which parents and caregivers accept vaccines for their children and agree for them to be vaccinated is complex and involves health providers, parents or other caregivers, and adolescents themselves. Better understanding about how each step in the process is influenced could lead to more effective interventions.

5. Determine How Best to Integrate HPV Vaccination With Cervical Cancer Screening

Though widespread adoption of HPV vaccines has potential to reduce cervical cancer incidence and mortality significantly, cervical cancer screening programs remain an essential part of cervical cancer control programs. However, with time, modification of screening practices likely will be warranted. As rates of infection with the most oncogenic forms of HPV decline, fewer abnormal screening tests will occur, and those that do occur likely will be due to low-grade lesions with low probability of progressing to invasive cancer. A higher proportion of abnormalities identified through screening could result in unnecessary clinical interventions associated with risks for patients as well as higher costs.[151,152]

Modification of screening guidelines may help reduce unnecessary risks and costs. Currently, women are advised to begin screening at age 21 and be screened every three to five years, depending on the testing used.[153-155] As vaccination diffuses across the population, it may be appropriate for women to begin screening at later ages, be screened less often, and/or move to primary HPV-based screening. Any modifications to screening guidelines must be based on solid evidence. As HPV vaccine use increases, research is needed to monitor population changes in risk of cervical cancer and precancers. Ideally, studies should determine how risks differ for unvaccinated women compared with women who were vaccinated prior to initiation of sexual activity. This type of research will benefit from highly integrated data systems that include linkages among immunization information systems, screening registries, and cancer registries.

Conclusions

HPV infections cause nearly 26,000 cases of cancer in the U.S. and more than 600,000 cases worldwide each year. Two safe, effective vaccines can prevent infections with HPV types most commonly associated with cancer. In the United States, these vaccines have been recommended by ACIP for adolescent girls since 2006 and for adolescent boys since 2011.* However, HPV vaccine uptake lags behind that of other adolescent vaccines, leaving millions of young people vulnerable to infection with this cancer-causing virus.

Increasing HPV vaccine uptake in the United States should be a public health priority. Successes in other countries and in parts of the United States indicate that this goal is achievable. Targeted interventions are needed to ensure timely progress. In this report, the Panel outlined a multipronged strategy for accelerating U.S. HPV vaccine uptake. All stakeholders in the National Cancer Program should work together and with stakeholders focused on vaccines to promote and facilitate HPV vaccination as an urgent national priority.

Key to increasing HPV vaccination in the U.S. is reducing missed clinical opportunities. If all providers strongly recommend HPV vaccines to age-eligible patients, including those receiving other vaccines, uptake of HPV vaccines should increase dramatically. Systems changes should be made, as necessary, to support this recommendation. Also, parents and adolescents should be provided with information about HPV-associated diseases and vaccines so they can make informed decisions. In addition, they should be able to obtain vaccines at convenient locations and from a wider range of providers, including pharmacists.

Although the Panel's charge is focused on the U.S. National Cancer Program, the Panel recognizes the role of the United States in supporting cancer control efforts in other parts of the world, particularly low- and middle-income countries. Moreover, especially in the case of infectious diseases, what happens in one country may influence the health of another. HPV vaccines have the potential to reduce the significant burden of cervical cancer and other HPV-associated cancers in these countries. The United States should continue to collaborate with global partners and find ways to support development of HPV vaccine programs around the world.

Continued research on HPV-associated cancers and HPV vaccines is needed to ensure that messages regarding vaccination are effective and that current vaccines are used optimally. Evidence that one or two doses are effective likely would result in major increases in HPV vaccine uptake. Next-generation vaccines that offer broader protection and/or logistical advantages should be pursued. Research is needed to determine how best to integrate HPV vaccination and cervical cancer screening.

The Panel is committed to achieving the vision of increased HPV vaccine uptake. In that spirit, the Panel suggests that a credible organization, such as NVAC, be given responsibility for monitoring the status of uptake and implementation of these recommendations. That accountability, in combination with the Panel's commitment to monitor implementation of recommendations outlined in this report, will increase the likelihood that the report and its recommendations will become agents for change. The ultimate goal is reduction, or even elimination, of preventable HPV-associated cancers in the United States and around the world. This is a goal around which all major cancer and vaccine-related organizations should rally. It is achievable and within our reach.

* The ACIP recommendation for males is for Gardasil® only.

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Appendices

Appendix A: Workshop Dates and Roster of Participants

Meeting Date	Location
July 24, 2012	San Francisco, CA
September 13, 2012	Arlington, VA
November 16, 2012	Chicago, IL
April 23-24, 2013	Miami, FL

Meeting Participants	Affiliations
Jan Agosti, MD	Bill & Melinda Gates Foundation
Kenneth A. Alexander, MD, PhD	The University of Chicago
Rachel Ballard-Barbash, MD, MPH	U.S. National Cancer Institute
Joan Benson, MD	Merck & Co., Inc.
F. Javier Bosch Jose, MD, PhD	Catalan Institute of Oncology (Institut Català d'Oncologia—ICO), Spain
Michael T. Brady, MD	Nationwide Children's Hospital
Noel T. Brewer, PhD	University of North Carolina Gillings School of Global Public Health Lineberger Comprehensive Cancer Center
Karen Canfell, PhD	The University of New South Wales, Australia
Philip Castle, PhD, MPH	Global Cancer Initiative
Tania Cernuschi, MS	GAVI Alliance, Switzerland
Victoria Champion, PhD, RN, FAAN	Indiana University
David Chelmow, MD	Virginia Commonwealth University
Janine Cory, MPH	U.S. Centers for Disease Control and Prevention
Tamera Coyne-Beasley, MD, MPH	University of North Carolina School of Medicine
Robert T. Croyle, PhD	U.S. National Cancer Institute
Kevin Cullen, MD	University of Maryland Greenebaum Cancer Center
Amanda Dempsey, MD, PhD, MPH	University of Colorado School of Medicine
Gary Dubin, MD	GlaxoSmithKline Vaccines
F. Reed Dulany, III	Dulany Industries, Inc.
Donatus U. Ekwueme, PhD	U.S. Centers for Disease Control and Prevention
Neal Fowler, MBA	Liquidia Technologies
Eduardo L. Franco, DrPH	McGill University, Canada
Denise A. Galloway, PhD	Fred Hutchinson Cancer Research Center
Maurice Gatera, MPH candidate	Rwanda Biomedical Center, Rwanda
Bruce G. Gellin, MD, MPH	U.S. Department of Health and Human Services

Meeting Participants	Affiliations
Maura L. Gillison, MD, PhD	James Cancer Hospital and Comprehensive Cancer Center The Ohio State University
Venus Ginés, MPH	Dia de La Mujer Latina Baylor College of Medicine
Marc T. Goodman, PhD, MPH	Samuel Oschin Comprehensive Cancer Institute Cedars-Sinai Medical Center
Hill Harper, JD	President's Cancer Panel Author, Actor, and Philanthropist
Richard M. Haupt, MD, MPH	Merck & Co., Inc.
Rolando Herrero, MD, PhD	International Agency for Research on Cancer, France
Allan Hildesheim, PhD	U.S. National Cancer Institute
Therese Hoyle, BSHE	Hoyle Consulting, Inc.
Lenora E. Johnson, DrPH	U.S. National Cancer Institute
Nathalia Katz, MD	Ministry of Health, Argentina
Judith S. Kaur, MD	Mayo Comprehensive Cancer Center
Rima F. Khabbaz, MD	U.S. Centers for Disease Control and Prevention
Jane Kim, PhD	Harvard School of Public Health
D. Scott LaMontagne, PhD, MPH, FRSPH	University of Washington School of Public Health PATH
Eduardo Lazcano, MD, PhD	National Institute of Public Health, Mexico
Julie Leask, PhD, MPH	National Centre for Immunisation Research & Surveillance, Australia
Douglas R. Lowy, MD	U.S. National Cancer Institute
Lauri E. Markowitz, MD	U.S. Centers for Disease Control and Prevention
Daniel M. Meyer, DDS	American Dental Association
Amy B. Middleman, MD, MSEd, MPH	Texas Children's Hospital Baylor College of Medicine
Olufunmilayo I. Olopade, MD, FACP	The University of Chicago Medicine
Joel Palefsky, MD	University of California, San Francisco School of Medicine
Marcus Plescia, MD, MPH	U.S. Centers for Disease Control and Prevention
Cynthia M. Rand, MD, MPH	University of Rochester Medical Center
Barbara K. Rimer, DrPH	President's Cancer Panel University of North Carolina Gillings School of Global Public Health
Jeff Roberts, MD	U.S. Food and Drug Administration
Daniel Rodriguez, MBA	Pan American Health Organization
Mitchel C. Rothholz, RPh, MBA	American Pharmacists Association

Meeting Participants	Affiliations
Abby B. Sandler, PhD	President's Cancer Panel U.S. National Cancer Institute
Mona Saraiya, MD, MPH	U.S. Centers for Disease Control and Prevention
Debbie Saslow, PhD	American Cancer Society
Mark Schiffman, MD, MPH	U.S. National Cancer Institute
Nathalie Schrameijer, MD	GlaxoSmithKline Biologicals
Anne Schuchat, MD	U.S. Centers for Disease Control and Prevention
Jennifer S. Smith, PhD, MPH	University of North Carolina Gillings School of Global Public Health
Diane Solomon, MD	U.S. National Cancer Institute
Shannon Stokley, MPH	U.S. Centers for Disease Control and Prevention
John Strand, MEd	FHI 360
Stephen Taplin, MD, MPH	U.S. National Cancer Institute
Edward Trimble, MD, MPH	U.S. National Cancer Institute
Elizabeth R. Unger, MD, PhD	U.S. Centers for Disease Control and Prevention
Claudia Vellozzi, MD, MPH	U.S. Centers for Disease Control and Prevention
Susan A. Wang, MD, MPH	World Health Organization, Switzerland
Cosette M. Wheeler, PhD	University of New Mexico School of Medicine
Owen N. Witte, MD	President's Cancer Panel University of California, Los Angeles

Appendix B: President's Cancer Panel Recommendations and Responsible Stakeholders

Goals and Objectives	Responsible Stakeholder(s) and Other Entities
Goal 1: Reduce Missed Clinical Opportunities to Recommend and Administer HPV Vaccines	
Objective 1.1: CDC should develop, test, disseminate, and evaluate the impact of integrated, comprehensive communication strategies for physicians and other relevant health professionals.	Centers for Disease Control and Prevention
Objective 1.2: Providers should strongly encourage HPV vaccination of age-eligible males and females whenever other vaccines are administered.	Healthcare providers Health professionals organizations (e.g., American Academy of Pediatrics, American Academy of Family Physicians, American College of Obstetricians and Gynecologists, Society for Adolescent Health and Medicine)
Objective 1.3: Healthcare organizations and practices should use electronic office systems, including electronic health records (EHRs) and immunization information systems (IIS), to avoid missed opportunities for HPV vaccination.	Centers for Disease Control and Prevention Health professionals organizations (e.g., American Academy of Pediatrics, American Academy of Family Physicians, American College of Obstetricians and Gynecologists, Society for Adolescent Health and Medicine)
Objective 1.4: Healthcare payers should reimburse providers adequately for HPV vaccines and for vaccine administration and services.	Health insurance companies America's Health Insurance Plans Medicaid Healthcare organizations
Objective 1.5: The current Healthcare Effectiveness Data and Information Set (HEDIS) quality measure for HPV vaccination of adolescent females should be expanded to include males.	National Committee for Quality Assurance
Objective 1.6: Create a *Healthy People 2020* HPV vaccination goal for males.	U.S. Department of Health and Human Services
Goal 2: Increase Parents', Caregivers', and Adolescents' Acceptance of HPV Vaccines	
Objective 2.1: CDC should develop, test, and collaborate with partner organizations to deploy integrated, comprehensive communication strategies directed at parents and other caregivers, and also at adolescents.	Centers for Disease Control and Prevention

Goal 3: Maximize Access to HPV Vaccination Services	
Objective 3.1: Promote and facilitate HPV vaccination in venues outside the medical home.	State and local health departments State legislatures American Pharmacists Association
Objective 3.2: States should enact laws and implement policies that allow pharmacists to administer vaccines to adolescents, including younger adolescents.	State legislatures Health professionals organizations (e.g., American Academy of Pediatrics, American Academy of Family Physicians, American College of Obstetricians and Gynecologists, Society for Adolescent Health and Medicine) American Pharmacists Association
Objective 3.3: Overcome remaining barriers to paying for HPV vaccines, including payment for vaccines provided outside the medical home and by out-of-network or nonphysician providers.	Health insurance companies, health insurance exchanges America's Health Insurance Plans State insurance commissions
Goal 4: Promote Global HPV Vaccine Uptake	
Objective 4.1: The United States should continue its collaboration with and support of GAVI to facilitate HPV vaccine introduction and uptake in low-income countries.	The President Congress U.S. Department of Health and Human Services • Centers for Disease Control and Prevention • National Cancer Institute U.S. Agency for International Development
Objective 4.2: The United States should continue to support global efforts to develop comprehensive cancer control plans and cancer registries in low- and middle-income countries.	The President Congress U.S. Department of Health and Human Services • Centers for Disease Control and Prevention • National Cancer Institute
High-Priority Research to Advance Prevention of HPV-Associated Cancers	
	U.S. Department of Health and Human Services • Centers for Disease Control and Prevention • National Institutes of Health Pharmaceutical and biotechnology companies Other public and private funders of biomedical research

Appendix C: Recommendations and Goals Relevant to HPV Vaccination

Recommendations or Policy Statements Regarding HPV Vaccination	
Advisory Committee on Immunization Practices	Centers for Disease Control and Prevention. Human papillomavirus (HPV) ACIP vaccine recommendations [Internet]. Atlanta (GA): CDC; [updated 2013 Jul 16; cited 2013 Sep 10]. Available from: http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html
American Academy of Family Physicians	American Academy of Family Physicians. Policies: immunizations [Internet]. Leawood (KS): AAFP; [cited 2013 Aug 20]. Available from: http://www.aafp.org/about/policies/all/immunizations.html
American Academy of Pediatrics	HPV vaccine recommendations. Pediatrics. 2012;129(3):602-5.
American Cancer Society	American Cancer Society. American Cancer Society recommendations for human papillomavirus (HPV) vaccine use to prevent cervical cancer and pre-cancers [Internet]. Atlanta (GA): ACS; [updated 2013 Apr 10; cited 2013 Sep 10]. Available from: http://www.cancer.org/cancer/cancercauses/othercarcinogens/infectiousagents/hpv/acs-recommendations-for-hpv-vaccine-use Saslow D, Castle PE, Cox JT, Davey DD, Einstein MH, Ferris DG, et al. American Cancer Society guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. CA Cancer J Clin. 2007;57(1):7-28.
American College of Obstetricians and Gynecologists	The American College of Obstetricians and Gynecologists Committee on Adolescent Health Care. Human papillomavirus vaccination. Committee Opinion No. 467. Obstet Gynecol. 2010 Sep;116:800-3.
Centers for Disease Control and Prevention	Centers for Disease Control and Prevention. HPV vaccine information for clinicians: fact sheet [Internet]. Atlanta (GA): CDC; [updated 2012 Jul 12; cited 2013 Sep 27]. Available from: http://www.cdc.gov/std/hpv/stdfact-hpv-vaccine-hcp.htm
Society for Adolescent Health and Medicine	Friedman LS, Kahn J, Middleman AB, Rosenthal SL, Zimet GD. Human papillomavirus (HPV) vaccine: a position statement of the Society for Adolescent Medicine. J Adolesc Health. 2006;39(4):620.
World Health Organization	World Health Organization. Human papillomavirus vaccines WHO position paper. Wkly Epidemiol Rec. 2009 Apr 10;84:117-32.
Goals for HPV Vaccination	
Healthy People 2020	U.S. Department of Health and Human Services. *Healthy People 2020*: immunization and infectious diseases objectives. [Internet]. Washington (DC): DHHS; [updated 2013 Apr 24; cited 2013 Jul 26]. Available from: http://www.healthypeople.gov/2020/topicsobjectives2020/objectiveslist.aspx?topicId=23

Recommendations or Strategies for Increasing Vaccination (not specific to HPV)	
American Academy of Pediatrics	American Academy of Pediatrics. Adolescent immunizations: strategies for increasing coverage rates [Internet]. Elk Grove Village (IL): AAP; [updated 2013 Jul; cited 2013 Aug 17]. Available from: http://www2.aap.org/immunization/pediatricians/pdf/TopStrategiesforIncreasingCoverage.pdf
National Vaccine Advisory Committee	Stokley S, Freed G, Curtis R, Gordon L, Humiston S, Parnell T, et al. Adolescent vaccination: recommendations from the National Vaccine Advisory Committee. Am J Prev Med. 2009;36(3):278-9.e6. Lindley M, Orenstein W, Shen A, Rodewald L, Birkhead G. Assuring vaccination of children and adolescents without financial barriers: recommendations from the National Vaccine Advisory Committee (NVAC). Washington (DC): U.S. Department of Health and Human Services; 2009 Mar 2. Available from: http://www.hhs.gov/nvpo/nvac/nvacfwgreport.pdf
National Vaccine Program Office	U.S. Department of Health and Human Services. 2010 national vaccine plan: protecting the nation's health through immunization. Washington (DC): DHHS. Available from: http://www.hhs.gov/nvpo/vacc_plan/2010%20Plan/nationalvaccineplan.pdf
Task Force on Community Preventive Services	Community Preventive Services Task Force. Guide to Community Preventive Services. Increasing appropriate vaccination [Internet]. Atlanta (GA): the Task Force; [updated 2013 Aug 5; cited 2013 Sep 14]. Available from: http://www.thecommunityguide.org/vaccines/index.html

Appendix D: Acronyms and Abbreviations

ACIP	Advisory Committee on Immunization Practices
ARRA	American Recovery and Reinvestment Act
CDC	Centers for Disease Control and Prevention
DHHS	Department of Health and Human Services
EHR	Electronic Health Record
FDA	Food and Drug Administration
GICR	Global Initiative for Cancer Registry Development in Low- and Middle-Income Countries
GNI	Gross National Income
HEDIS	Healthcare Effectiveness Data and Information Set
HIC	Higher-Income Country
HITECH	Health Information Technology for Economic and Clinical Health
HPV	Human Papillomavirus
IARC	International Agency for Research on Cancer
IDB	Islamic Development Bank
IIS	Immunization Information System
LMIC	Low- and Middle-Income Country
NCD	Noncommunicable Disease
NCI	National Cancer Institute
NCQA	National Committee for Quality Assurance
NIH	National Institutes of Health
NIS-Teen	National Immunization Survey-Teen
NVAC	National Vaccine Advisory Committee
PCP	President's Cancer Panel
PEPFAR	President's Emergency Plan for AIDS Relief
RRP	Recurrent Respiratory Papillomatosis
Tdap	Tetanus, Diphtheria, Pertussis
VFC	Vaccines for Children
VLP	Virus-Like Particle
WHO	World Health Organization

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Maximizing Our Nation's Investment in Cancer. Bethesda, MD: National Cancer Institute, 2008.

Reducing Environmental Cancer Risk: What We Can Do Now. Bethesda, MD: National Cancer Institute, 2010.

America's Demographic and Cultural Transformation: Implications for Cancer. Bethesda, MD: National Cancer Institute, 2011.

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