A Report to the President of the United States
from the Chair of the President's Cancer Panel

HPV VACCINATION FOR CANCER PREVENTION:

Progress, Opportunities, and a Renewed Call to Action

November 2018

THE PRESIDENT'S CANCER PANEL

CHAIR

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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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HPV Vaccination for Cancer Prevention: Progress, Opportunities, and a Renewed Call to Action

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The President
The White House
Washington, DC 20500

Dear Mr. President,

Today, there are safe and effective vaccines against human papillomavirus (HPV), a group of viruses that cause six cancers and other diseases. This extraordinary tool could prevent hundreds of thousands of cancers globally.

The President's Cancer Panel concluded in its 2012-2013 report that underuse of HPV vaccines is a serious but correctable threat to progress against cancer and identified several goals and objectives to help increase HPV vaccine uptake in the United States and globally. This report describes the notable progress made over the past five years and presents priorities and strategies to speed progress toward goals identified in the previous report.

Although vaccine uptake has improved in recent years, the fact remains that less than 50% of boys and girls in the United States are fully vaccinated against HPV. We are still far short of the government's *Healthy People 2020* goal of 80% of age-eligible adolescents. This target is achievable with the continued work and support of federal agencies, organizations, healthcare providers, and researchers.

Cancer and immunization partners have risen to the challenge of accelerating HPV vaccine uptake. They have raised awareness among the general public of the importance of HPV vaccination, supported healthcare providers and systems in delivering the HPV vaccine, and contributed to global efforts to promote HPV vaccination. However, much work remains to maximize the cancer prevention potential of HPV vaccination. It is critical that partnerships and collaborations are supported and expanded to drive further increases needed in HPV vaccine coverage.

The United States and stakeholders across the globe should renew their commitment to prioritize HPV vaccination. We have a chance to prevent cancers caused by HPV, an opportunity that should not be missed. Our children and future generations are counting on us to act now to protect them from deadly vaccine-preventable cancers. This is a win for individuals and families. I hope that you and your administration will encourage uptake of HPV vaccines.

Sincerely,

Barbara K. Rimer, DrPH
Chair
President's Cancer Panel

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EXECUTIVE SUMMARY

Human papillomaviruses (HPV) cause six types of cancer—cervical, oropharyngeal, anal, penile, vulvar, and vaginal—and several other diseases. HPV vaccination provides a compelling opportunity to protect against infection with HPV and prevent cancers and other diseases. The President's Cancer Panel concluded in its 2012-2013 report to the White House, *Accelerating HPV Vaccine Uptake: Urgency for Action to Prevent Cancer*, that underuse of HPV vaccines was a serious but correctable threat to progress against cancer. That report identified several goals and objectives to increase HPV vaccine uptake in the United States and globally.

Substantial progress in HPV vaccine uptake has been achieved in recent years—the percentage of adolescents who started the HPV vaccine series increased an average of 5 points each year between 2013 and 2017. However, HPV vaccine coverage is still too low to achieve its cancer prevention potential. As of 2017, less than half of U.S. adolescents were fully vaccinated, far below the *Healthy People 2020* goal—full vaccination of 80 percent of adolescents aged 13-15 years. In addition, HPV vaccines are not included in the national vaccine programs of many low- and middle-income countries, where the vast majority of cervical cancer cases and deaths occur.

In this report, the Panel Chair provides an overview of progress made over the past five years and presents priorities and strategies to speed progress toward goals identified in the previous report. Several research priorities also are highlighted.

Goals and Opportunities to Increase HPV Vaccine Uptake

The Panel's 2012-2013 report identified three goals to increase HPV vaccine uptake in the United States. A fourth goal was to promote global HPV vaccine uptake. Research and discussions with key stakeholders on the current landscape of HPV cancers and HPV vaccination led the Panel Chair to conclude that the goals outlined in the previous report are still relevant. Priorities and strategies that will help achieve these goals are outlined below.

Partnerships and Collaborations Are Essential

The coalescence of a critical mass of dedicated stakeholders has created momentum and opportunity to achieve the goals outlined in this report. The Panel Chair urges continued stakeholder collaborations and partnerships in implementing proven strategies to increase vaccination rates among all populations to target levels.

Goal 1: Reduce Missed Clinical Opportunities to Recommend and Administer the HPV Vaccine.

Communication strategies and systems changes are essential to ensure that all eligible adolescents and young adults are offered the HPV vaccine when they visit their healthcare providers. Provider- and systems-level changes hold the greatest potential for eliminating missed clinical opportunities, normalizing HPV vaccination, and ensuring that U.S. adolescents and future generations are optimally protected from HPV cancers. As such, the Panel Chair urges healthcare providers to strongly recommend HPV vaccination for all eligible adolescents. In addition, health system leaders should make HPV vaccination a high, measurable priority.

Goal 2: Increase Parents' Acceptance of HPV Vaccination.

Communication campaigns and promotion of the HPV vaccine by a growing number of healthcare providers have contributed to recent progress in vaccination rates. However, more must be done to ensure that parents have access to clear, accurate information about the HPV vaccine. The Panel Chair encourages the Centers for Disease Control and Prevention, American Cancer Society, and other trusted organizations to continue to develop and deploy evidence-based communication campaigns to increase parents' acceptance of HPV vaccination.

Goal 3: Maximize Access to HPV Vaccination Services.

Ensuring that HPV vaccination is affordable and convenient for all U.S. adolescents will support optimal vaccine uptake. National, regional, and local efforts are needed to understand and address existing and potential barriers to access. While sources of private and public financing currently ensure that the vaccine's cost is covered for most adolescents, the Panel Chair asserts that insurance coverage for preventive services must be maintained to ensure that cost does not limit U.S. adolescents' access to HPV vaccination.

Goal 4: Promote Global HPV Vaccine Uptake.

The potential impact of HPV vaccination is greatest in less developed countries, where the vast majority of cervical cancer cases and deaths occur and HPV vaccination rates are disproportionately low. The Panel Chair urges the United States to continue to support implementation and sustainability of HPV vaccination programs around the world, particularly in low- and middle-income countries.

A Renewed Call to Action

Progress and momentum built over the past half decade have created a compelling opportunity to further increase HPV vaccine uptake and dramatically reduce—and perhaps eventually largely eliminate—the preventable burden of HPV cancers. Cancer and immunization stakeholders worldwide must renew their collective commitment to achieving HPV vaccination targets. All should rally without hesitation around the ultimate goal of cancer prevention.

Research Priorities

- Establish natural history of oral HPV infections and develop tools to detect precancers.
- Understand and address inequities among populations with high rates of HPV cancers.
- Identify ways to harness social media to communicate about HPV and HPV vaccination.
- Determine efficacy and duration of protection of a single HPV vaccine dose.

PREFACE

The President's Cancer Panel (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 and presents findings and recommendations in reports to the President of the United States.

In 2012-2013, the Panel held a series of meetings on human papillomavirus vaccination. At that time, the Panel concluded that underuse of HPV vaccines was a serious but correctable threat to progress against cancer and identified several goals and objectives to increase HPV vaccine uptake in the United States and globally. Many stakeholders have worked resolutely to make progress toward these goals and to achieve the ultimate goal of preventing HPV cancers. The 2012-2013 Panel report is frequently cited as a seminal resource on HPV vaccination. In response to several stakeholders who have expressed interest in the Panel revisiting this topic, the Panel Chair has assessed the current landscape of HPV cancers and vaccination through consultations with experts about the state of the field, selective review of the literature, and additional research. In this report, the Panel Chair provides an overview of progress made over the past five years and presents priorities and strategies to speed progress toward goals identified in the 2012-2013 report.

While Panel reports are submitted to the President, they also are intended for use by a larger group of stakeholders, public and private, that comprise the National Cancer Program. As the Panel is advisory, implementation of Panel recommendations depends on actions of these stakeholders. Over the past five years, numerous organizations and agencies—including, but not limited to, the National Cancer Institute (NCI); NCI-designated cancer centers; Centers for Disease Control and Prevention; American Cancer Society; National HPV Vaccination Roundtable; American Academy of Pediatrics; American Academy of Family Physicians; World Health Organization; and Gavi, the Vaccine Alliance—have devoted substantial resources and voiced strong support for HPV vaccination. Progress to date is a testament to the dedicated efforts, strategic focus, and persistence of these organizations and their partners throughout the United States and globally. The United States and its global partners must seize the opportunity to build on this momentum to eliminate both the barriers to HPV vaccine uptake and the unnecessary burden of preventable HPV cancers.

THE CURRENT LANDSCAPE OF HPV CANCERS AND HPV VACCINATION

Human papillomaviruses cause nearly 630,000 cases of cancer worldwide each year. The majority—530,000—are cervical cancers, but HPV also is responsible for about 100,000 cancers at five other sites, including the oropharynx, anus, penis, vulva, and vagina.[1*] In 2006, the first HPV vaccine was approved, making available a powerful new tool for preventing cancers and other diseases caused by these viruses. Two additional HPV vaccines were approved in 2009 and 2014. Despite extensive evidence that these vaccines are remarkably effective and safe, early uptake was slow in the United States and some other countries.

In its 2012-2013 report, *Accelerating HPV Vaccine Uptake: Urgency for Action to Prevent Cancer*, the President's Cancer Panel concluded that underuse of HPV vaccines was a serious threat to progress against cancer and recommended several steps to increase vaccination in the United States and globally.[2] Other high-profile reports—including 2015 and 2018 reports from the National Vaccine Advisory Committee[3,4] and 2016 reports from the Cancer Moonshot Blue Ribbon Panel[5] and Cancer Moonshot Task Force[6]—echoed the Panel's call for action.

This report of the Panel Chair provides an update on the landscape of HPV cancers and HPV vaccination. Substantial progress in HPV vaccine uptake has been achieved in recent years—the percentage of adolescents who started the HPV vaccine series increased an average of 5 percentage points each year between 2013 and 2017.[7] This is a testament to the hard work and dedication of the many stakeholders who have come together to promote HPV vaccination. However, the United States and many other countries still fall far short of target vaccination rates.

On average, the percentage of adolescents who started the HPV vaccine series increased 5 percentage points each year between 2013 and 2017.

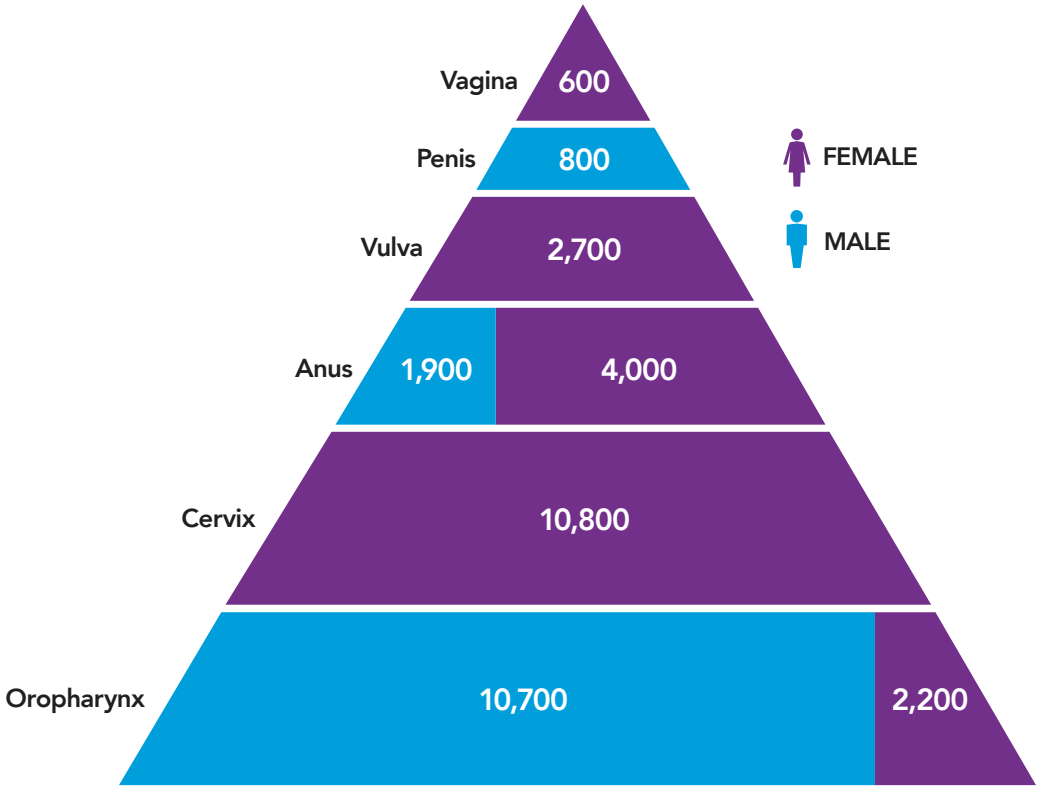
HPV Cancers Affect Thousands of U.S. Women and Men

There are more than 150 strains, or types, of HPV. In the United States, about 79 million people currently are infected with HPV, and about 14 million will become newly infected with HPV each year. Most sexually active men and women will be infected with HPV at some point in their lives if they do not receive the HPV vaccine.[8] The majority of HPV infections go away without treatment and do not cause health problems. In some cases, however, HPV infections persist and cause cancer and other diseases.

In the United States, HPV causes nearly 34,000 cases of cancer each year (Figure 1).[9] In addition, about 300,000

* de Martel et al. include cancers of the oral cavity and larynx in their estimate of HPV-attributable cancers. The U.S. Centers for Disease Control and Prevention has concluded that HPV causes some cancers of the oropharynx, but that the evidence that HPV causes cancers of the oral cavity and larynx is insufficient. Thus, numbers in this report include estimates for oropharyngeal but not oral cavity and laryngeal cancers.

Figure 1. Numbers of U.S. Cancers Caused by HPV



Source: Centers for Disease Control and Prevention. How many cancers are linked with HPV each year? [Internet]. Atlanta (GA): CDC; [updated 2018 Aug 22; cited 2018 Aug 26]. Available from: https://www.cdc.gov/cancer/hpv/statistics/cases.htm.

U.S. women undergo invasive treatment for cervical precancers caused by HPV.[10,11] Women are more likely than men to be diagnosed with HPV cancers, but the burden of HPV cancers among men is increasing. This trend is driven largely by increases in HPV-positive oropharyngeal cancers over the past three decades, particularly among men, even as incidence rates of other head and neck cancers and many other cancers are decreasing.[12-15] The number of oropharyngeal cancers attributed to HPV is now higher than the number of cervical cancers in the United States.[9,16]

Vaccines Protect Against Cancer-Causing HPV Types

When the 2012-2013 Panel report on HPV vaccination was released, two HPV vaccines were approved for use in the United States—Cervarix and Gardasil. Both vaccines are designed to protect against the two most common cancer-causing types of HPV—HPV 16 and HPV 18—which together account for about two-thirds of cervical cancers. Gardasil also protects against HPV 6 and 11, which cause genital warts and recurrent respiratory papillomatosis, a rare but debilitating disease characterized by noncancerous growths in the respiratory tract. Cervarix provides cross-protection against three additional cancer-causing HPV types (HPV 31, 33, and 45) that are related to HPV 16 or HPV 18.[17]

In 2014, the U.S. Food and Drug Administration (FDA) approved a third HPV vaccine—Gardasil 9—which protects against HPV 16, 18, 6, 11, and five additional cancer-causing HPV types (HPV 31, 33, 45, 52, 58).[18] The HPV types covered by Gardasil 9 cause the vast majority of HPV-associated diseases in the United States and worldwide.[19] Since January 2017, only Gardasil 9 has been available in the United States. Cervarix and Gardasil are still used in some other countries.

Two Vaccine Doses Are Sufficient to Protect Younger Adolescents

The Advisory Committee on Immunization Practices (ACIP) recommends routine HPV vaccination of girls and boys at 11 or 12 years of age.[20] Initial recommendations for girls (in 2006) and boys (in 2011) called for a three-dose series.[21-23] In 2016, ACIP updated its recommendation to indicate that adolescents who initiate the vaccine series before 15 years of age need only two doses (separated by 6-12 months).[20] This update, which aligns with the World Health Organization recommendation,[24] was based on evidence that two doses of the vaccine in younger adolescents produced an immune response similar to or higher than the response in young adults who received three doses.[25] ACIP also recommends vaccination for females through age 26 and for males through age 21 who were not adequately vaccinated previously. Vaccination for some special populations is recommended through 26 years of age.[20†]

HPV Vaccines Are Safe and Effective

HPV vaccines are safe. All three vaccines have excellent safety profiles based on clinical trials and postapproval monitoring and evaluation in the United States and other countries.[26-28] As of 2017, more than 270 million HPV vaccine doses had been distributed worldwide,[26] including over 100 million in the United States.[28] More than 100 studies that included 2.5 million people in 6 countries have found no serious adverse effects of HPV vaccination beyond what is typical for other adolescent vaccines.[27] The Centers for Disease Control and Prevention and the FDA continue to monitor the safety of these vaccines, as for all vaccines.

HPV vaccines are highly effective. In clinical trials, among women who were not previously infected with HPV, the vaccines provided nearly complete protection against persistent HPV infection and cervical, vaginal, and vulvar precancers caused by vaccine-targeted HPV types.[29-32] Women who were vaccinated as part of a clinical trial also had lower prevalence of oral HPV infections than did participants in the trial who were not vaccinated.[33]

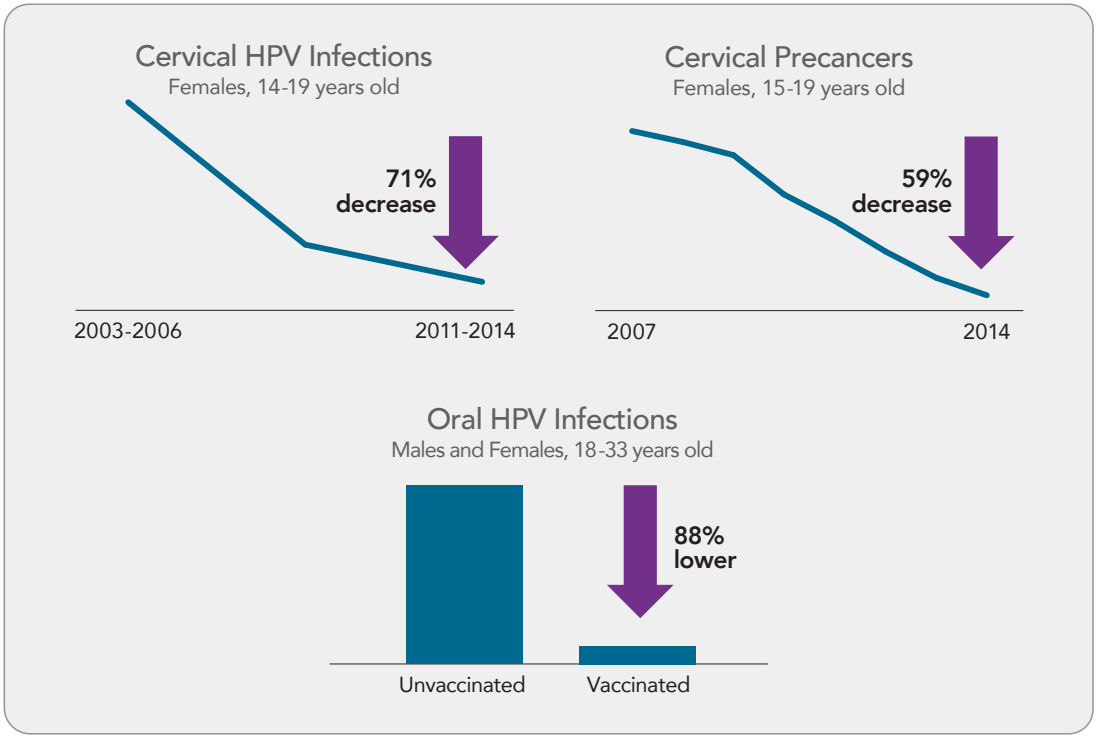
Rates of vaccine-type cervical HPV infections and HPV cervical precancers have declined in the United States (Figure 2) and many countries following implementation of HPV vaccination programs.[17, 34-43] Early evidence suggests that HPV vaccination may be contributing to recent declines in cervical cancer incidence among young females,[44,45] although further studies are needed to confirm these findings. In addition, lower rates of oral HPV infections have been documented among vaccinated compared with unvaccinated U.S. men and women (Figure 2).[46] Reductions in genital warts also have been observed in the years following introduction of the vaccine;[34] it is predicted that genital warts will be nearly eliminated in Australia as a result of HPV vaccination.[47]

Research Priority: Natural History of Oral HPV Infections

HPV vaccines are not currently approved for prevention of HPV-associated oropharyngeal cancers, but based on what is known about the biology of these cancers, it is highly likely the vaccines will be protective. To test whether HPV vaccination prevents oropharyngeal cancer, the natural history of oral HPV infections must be further elucidated and tools must be developed to allow detection of precancers.

† FDA recently expanded the approved use of Gardasil 9 to include men and women aged 27-45 years. An ACIP decision on whether to expand the recommended ages for vaccination is expected to occur in the future. Source: U.S. Food and Drug Administration. FDA approves expanded use of Gardasil 9 to include individuals 27 through 45 years old [News Release]. Silver Spring (MD): FDA; 2018 Oct 5. Available from: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm622715.htm

Figure 2. Prevalence of Cervical HPV Infection, Cervical Precancers, and Oral HPV Infection in the HPV Vaccine Era



Note: Cervical and oral infection data represent prevalence of HPV 16/18/6/11 among select National Health and Nutrition Examination Survey (NHANES) participants. Oral HPV infection prevalence is based on cross-sectional data from NHANES 2011-2014. Cervical precancer data represent prevalence of cervical intraepithelial neoplasia grades 2 and 3 among privately insured U.S. female adolescents and women. **Sources:** Oliver SE, Unger ER, Lewis R, et al. Prevalence of human papillomavirus among females after vaccine introduction-National Health and Nutrition Examination Survey, United States, 2003-2014. J Infect Dis. 2017;216(5):594-603; Flagg EW, Torrone EA, Weinstock H. Ecological association of human papillomavirus vaccination with cervical dysplasia prevalence in the United States, 2007-2014. Am J Public Health. 2016;106(12):2211-8; Chaturvedi AK, Graubard BI, Broutian T, et al. Effect of prophylactic human papillomavirus (HPV) vaccination on oral HPV infections among young adults in the United States. J Clin Oncol. 2018;36(3):262-7.

U.S. HPV Vaccine Uptake: Progress and Continuing Challenges

When the Panel's 2012-2013 report on HPV vaccination was released, the most recent data indicated that only one-third of 13- to 17-year-old females and fewer than 7 percent of males had received the recommended three doses.[48] Fortunately, there has been notable progress over the past five years.

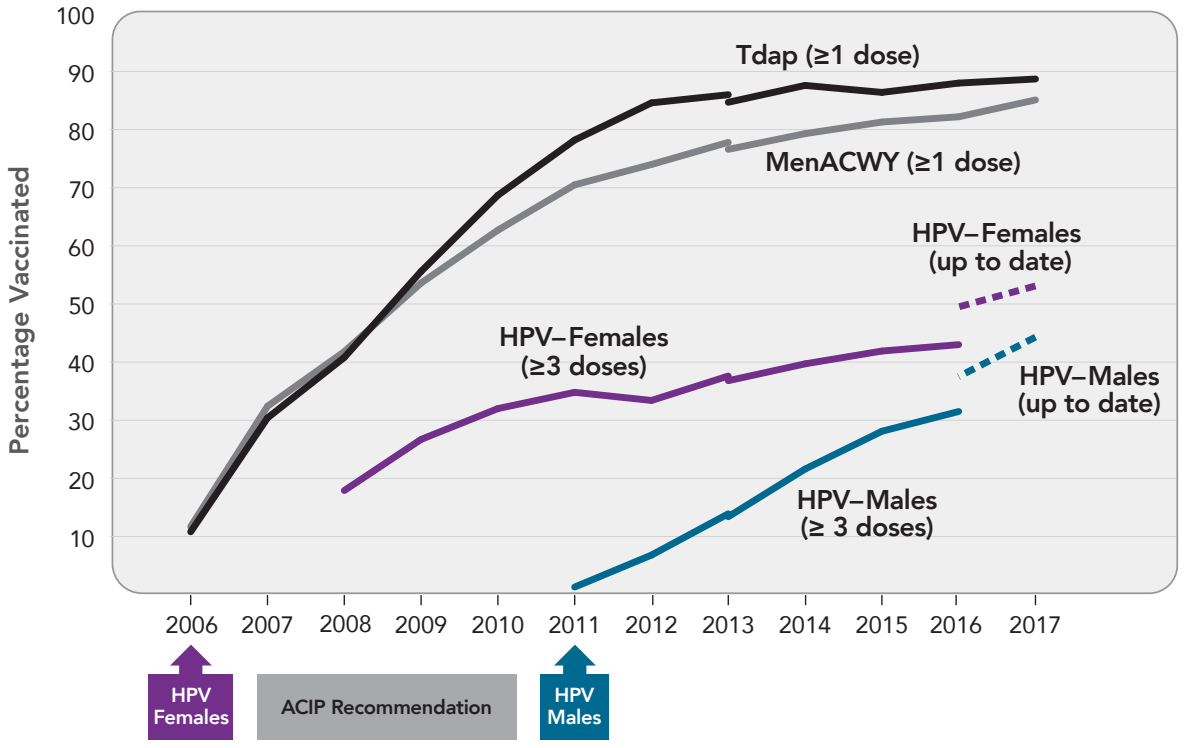
- **HPV vaccination has increased overall.** In 2017, among those 13 to 17 years old, over half of females (53%) and more than one-third of males (44%) were up to date with respect to HPV vaccination (at least two doses for those who received their first HPV vaccine dose before age 15 and at least three doses for others; Figure 3). More than 65 percent of adolescents in this age group had received at least one dose of the vaccine, an increase over earlier years.[7]

- **HPV vaccination of males has increased.** When the Panel's 2012-2013 report was released, vaccination coverage among adolescent boys lagged far behind that of girls, at least in part because the ACIP recommendation for boys was not issued until 2011. However, this gap is narrowing (Figure 3). Large increases in male vaccination rates have occurred across every stratum of age, race/ethnicity, and poverty level.[49]

- **HPV vaccination has increased dramatically in some states and regions.** In 2017, more than 80 percent of adolescents in two states (Rhode Island and Massachusetts) and the District of Columbia initiated the HPV vaccine series.[7] Between 2013 and 2017, the percentage of adolescents who received their first dose of the HPV vaccine doubled or nearly doubled in four states (Utah, Arkansas, Virginia, and Montana). An additional 25 states increased one-dose coverage by more than 50 percent during this time period.[7]

Specific examples of successful efforts and programs are described later in the report (see *Quality Improvement Initiative Improves HPV Vaccine Initiation and Completion* on page 14, *Rapid Adoption of the HPV Vaccine within a Health System* on page 15, and *School Program Increases HPV Vaccination in Rural North Dakota* on page 21). Despite this progress, U.S. HPV vaccination rates do not meet the *Healthy People 2020* goal—full vaccination of 80 percent of adolescents aged 13-15 years.[50] Several statistics highlight the need to increase HPV vaccination rates throughout the United States.

Figure 3. Vaccine Uptake Among U.S. Adolescents Aged 13-17 Years, 2006-2017



Note: Adolescents were considered to be up to date for HPV if they had received ≥3 doses, or if all of the following applied: 1) they had received two doses; 2) the first dose was received before the 15th birthday; and 3) the interval between the first and second doses was ≥5 months minus 4 days, the absolute minimum interval between the first and second doses. NIS-Teen implemented a revised adequate provider definition in 2013 and retrospectively applied this definition to 2013 data, which causes a shift in trendlines in 2013. **Source:** Walker TY, Elam-Evans LD, Yankey D, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13-17 years—United States, 2017. MMWR Morb Mortal Wkly Rep. 2018;67(33):909-17.

- **HPV vaccination coverage remains lower than that of other adolescent vaccines.** HPV is one of three vaccines recommended for adolescents at age 11-12 years—the other two are the tetanus, diphtheria, and acellular pertussis vaccine (Tdap) and the meningococcal conjugate vaccine (MenACWY). In 2017, nearly 90 percent of 13- to 17-year-old adolescents received the Tdap vaccine, and 85 percent received the initial dose of MenACWY vaccine; however, only 49 percent had received all recommended doses of the HPV vaccine.[7]

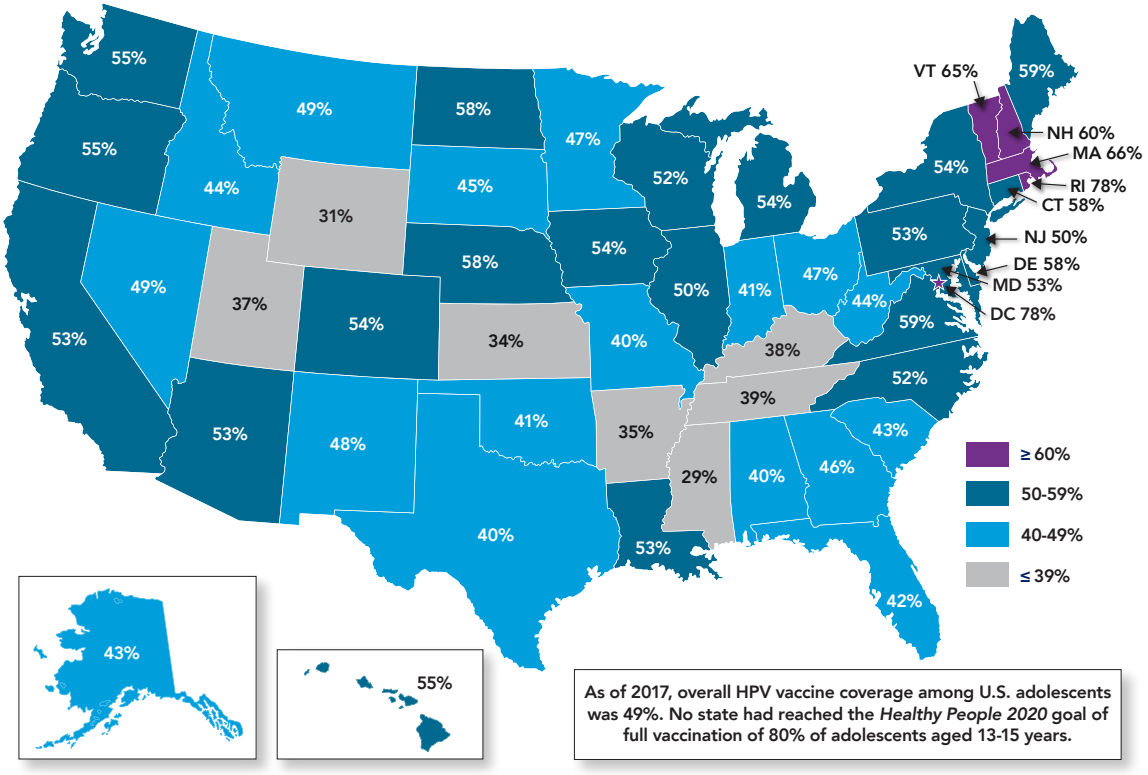
- **HPV vaccination coverage in the United States remains lower than in other countries.** In Australia, in 2016, 79 percent of females and 73 percent of males had received three doses of the HPV vaccine by 15 years of age.[51,52] In the United Kingdom, in 2016-2017, 83 percent of 13- to 14-year-old females had completed the two-dose HPV vaccination series.[53] In the United States, however, among 13- to 17-year-olds, only 53 percent of females and 44 percent of males had received all recommended doses.[7]

- **HPV vaccine uptake is uneven across the United States.** HPV vaccination coverage varies substantially by state (Figure 4)—rates of up-to-date HPV vaccination range from a low of 29 percent in Mississippi to a high of 78 percent in the District of Columbia.[7] No state or region has achieved the nation's goal of full vaccination of 80 percent of adolescents. HPV vaccination rates are particularly low in rural areas, despite high uptake of other adolescent vaccines; over half of adolescents in urban areas are up to date on their HPV vaccination compared with only 42 percent in rural areas.[7] There also are differences in vaccine uptake by race/ethnicity, socioeconomic status, and insurance status. The reasons for differences between populations are not fully understood.

Research Priority: Understanding and Addressing Inequities

Research is needed to elucidate factors that contribute to lower HPV vaccination rates among populations with disproportionately high rates of HPV cancers (e.g., rural). Investments in implementation research could inform development and scale-up of interventions targeting these populations.

Figure 4. Rates of Up-to-Date HPV Vaccination Among U.S. Adolescents Aged 13-17 Years, 2017



Source: Walker TY, Elam-Evans LD, Yankey D, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13-17 years—United States, 2017. MMWR Morb Mortal Wkly Rep. 2018;67(33):909-17.

GOALS AND OPPORTUNITIES TO INCREASE HPV VACCINE UPTAKE

The Panel's 2012-2013 report identified three goals to increase HPV vaccine uptake in the United States: reduce missed clinical opportunities for HPV vaccination, increase parents' acceptance of the vaccine, and maximize access to HPV vaccination. A fourth goal was to promote global HPV vaccine uptake. While there has been progress toward these goals, HPV vaccine coverage is still too low to achieve its cancer prevention potential. The benefits of HPV vaccination have become even more evident over the past five years. Several organizations—including the World Health Organization, American Cancer Society (ACS), NCI-designated cancer centers, and International Papillomavirus Society—have concluded that HPV vaccination could dramatically reduce or even eliminate cervical cancer as a public health problem when used in combination with cancer screening.[54-58]

Research and discussions with key stakeholders on the current landscape of HPV cancers and HPV vaccination led the Panel Chair to conclude that the goals outlined in the 2012-2013 report are still relevant. The following sections describe priorities and strategies—informed by research and real-world experiences over the past five years—that will help achieve these goals. Several research priorities also are highlighted throughout the report, complementing research gaps that have been identified by others.[59]

The coalescence of a critical mass of dedicated stakeholders (see *Partnerships and Collaborations Are Essential to Promote HPV Vaccine Uptake* on page 10), accumulation of data on the benefits of HPV vaccination, and increasing awareness and acceptance of the vaccines among healthcare providers and the public has created momentum and opportunity to achieve the goals outlined in this report. This opportunity must be seized to accelerate HPV vaccine uptake and achieve the potential of vaccination to reduce dramatically the number of HPV cancers in the United States and around the world. Efforts to increase HPV vaccination should consider the changing landscape of healthcare delivery in the United States. Trends such as the increasing popularity of retail clinics[60] and the consolidation of providers within larger healthcare systems[61] may present both challenges to and opportunities for increasing HPV vaccination.

Partnerships and Collaborations Are Essential to Promote HPV Vaccine Uptake

In its earlier report, the Panel stated that increasing HPV vaccine levels would require concerted action by multiple organizations and individuals. Since that time, many key stakeholders have forged or enhanced collaborations and partnerships to identify and take concrete steps to address barriers to HPV vaccination. These have included unprecedented partnerships among cancer control and immunization experts. A few examples of partnerships and collaborations—catalyzed, in part, by the 2012-2013 Panel report—are described below.

The Panel Chair urges continued stakeholder collaborations and partnerships in implementing proven strategies to increase vaccination rates among all populations to target levels. Local and regional partnerships will be particularly important for identifying local barriers and solutions to HPV vaccine uptake. Partner organizations should include state immunization and cancer control programs, state cancer plans, providers and provider organizations, survivors, advocacy organizations, vaccine manufacturers, and others. The Centers for Disease Control and Prevention (CDC), National Cancer Institute (NCI), and other funding organizations should continue to support partnerships and collaborations aimed at HPV vaccination.

National HPV Vaccination Roundtable

The National HPV Vaccination Roundtable—hosted by the American Cancer Society and funded in large part by CDC—was formed in 2015 to convene stakeholders, facilitate information exchange, identify gaps, and catalyze efforts to increase U.S. HPV vaccine coverage. More than 75 organizations representing public health, academia, advocacy organizations, professional societies, industry, and state and federal agencies participate in the Roundtable. Task groups bring together member organizations to work on key topics, such as provider training and state HPV coalitions. The Roundtable also maintains a resource library with materials for a variety of stakeholders and audiences.

NCI-Designated Cancer Centers

The NCI Cancer Centers Program provides support for 70 centers across the country that meet rigorous standards for transdisciplinary research programs focused on developing new and improved approaches for cancer prevention, diagnosis, and treatment. In July 2014, NCI provided supplemental funding to 18 NCI-designated cancer centers to help address HPV vaccination in their respective catchment areas. Each cancer center conducted an environmental scan to identify local barriers and facilitators to HPV vaccination and developed linkages with existing coalitions and programs in the state or region (e.g., healthcare providers, health departments, immunization coalitions).

Although funding was for only one year, the cancer centers have maintained their commitment to increasing HPV vaccination. Each year since 2015, a different cancer center has hosted a meeting to enable centers to learn from and work with one another. State and regional coalitions formed during the funding period—including the Alabama HPV Vaccination Coalition and the Intermountain West HPV Vaccination Coalition—are still active. NCI provided funding to an additional 12 cancer centers in 2017 to promote HPV vaccine uptake.

Sources: Saslow D, Sienko J, Nkonga JLZ, Brewer NT. Creating a National Coalition to Increase Human Papillomavirus Vaccination Coverage. Acad Pediatr. 2018;18(2S):S11-S3; National HPV Vaccination Roundtable. Home page [Internet]. Atlanta (GA): the Roundtable; [cited 2018 Jul 6]. Available from: http://hpvroundtable.org/; National Cancer Institute Division of Cancer Control and Population Sciences. Administrative supplements for NCI-designated cancer centers to support collaborations to enhance HPV vaccination in pediatric settings: a summary report. Bethesda (MD): NCI DCCPS; 2016 Jun. Available from: https://healthcaredelivery.cancer.gov/hpvuptake/DCCPS_HPVvax-report_FINAL_508compliant.pdf; National Cancer Institute. HPV vaccine uptake in cancer centers [Internet]. Bethesda (MD): NCI; [cited 2018 Jul 6]. Available from: https://healthcaredelivery.cancer.gov/hpvuptake

Goal 1

Reduce Missed Clinical Opportunities to Recommend and Administer the HPV Vaccine.

In its 2012-2013 report, the Panel recommended development of communication strategies and systems changes to ensure that all eligible adolescents and young adults were offered the HPV vaccine when they visited their healthcare providers. Since that time, the Centers for Disease Control and Prevention (CDC) launched a multipronged campaign aimed at improving clinicians' practices, recognizing HPV vaccine champions, and supporting health systems.[62-64] The American Academy of Pediatrics (AAP), American Academy of Family Physicians (AAFP), and other health professional associations have urged their members to recommend vaccination strongly and developed resources to support increases in uptake (see *Professional Organizations Urge Strong Recommendations* below).[65-69] Several interventions targeting provider HPV vaccine knowledge and practices also have been developed.[70,71]

The commitment of these groups and the efforts of many healthcare providers undoubtedly have contributed to increases in HPV vaccination observed in recent years. Their roles in progress achieved to date should be commended. Yet, too many adolescents continue to leave their doctors' offices without receiving the HPV vaccine, even when they have received other recommended vaccines.[7,72-74] One study of girls who had not received the HPV vaccine by 13 years of age found that 80 percent had had healthcare encounters during which another vaccine was administered.[73] If the HPV vaccine had been given at all of these visits, HPV vaccine initiation rates would have reached nearly 90 percent. **The Panel Chair emphasizes strongly that provider- and systems-level changes hold the greatest potential for eliminating missed clinical opportunities, normalizing HPV vaccination, and ensuring that U.S. adolescents and future generations are optimally protected from HPV cancers.**[75]

CDC, AAP, AAFP, and others have effectively promoted HPV vaccination through provider education, training, and resource development.

Professional Organizations Urge Strong Recommendations

In 2014, several health professional organizations—the American Academy of Family Physicians, American Academy of Pediatrics, American College of Obstetricians and Gynecologists, and American College of Physicians—partnered with the Centers for Disease Control and Prevention and Immunization Action Coalition to urge their members to firmly and strongly recommend HPV vaccination to their patients. Many providers reported improving their HPV vaccine communication after receiving information from their professional organizations.

Sources: American Academy of Family Physicians, American Academy of Pediatrics, American College of Obstetricians and Gynecologists, American College of Physicians, Centers for Disease Control and Prevention, Immunization Action Coalition. Letter to: Colleagues 2014. Available from: http://www.immunize.org/letter/recommend_hpv_vaccination.pdf; Hswen Y, Gilkey MB, Rimer BK, Brewer NT. Improving physician recommendations for human papillomavirus vaccination: the role of professional organizations. Sex Transm Dis. 2017;44(1):42-7.

Strong Provider Recommendations Are Needed

Provider recommendation is one of the strongest predictors of adolescent HPV vaccine uptake, even stronger than often-studied factors such as race/ethnicity, insurance status, knowledge of HPV, and perceptions about HPV vaccine effectiveness and safety.[76,77] Most physicians who provide care for adolescents say they recommend HPV vaccination,[78,79] and surveys of parents suggest that providers are more likely to recommend the HPV vaccine now than in the past.[80,81] However, too many parents of age-eligible adolescents do not recall receiving a recommendation from their children's healthcare providers.[77,80,81]

How the vaccine is recommended is important. Studies have found that providers often deliver weak or unclear recommendations for the HPV vaccine (e.g., presenting the vaccine as being optional, less important, or less urgent than other adolescent vaccines).[76,77,82,83] These recommendations may be sufficient for parents who already hold favorable views of HPV vaccination, but they are less likely to convince parents who have questions or uncertainties to vaccinate their adolescents.

CDC urges providers to deliver a clear, concise, and strong recommendation for same-day HPV vaccination.[62] The vaccine's efficacy in preventing cancer should be emphasized.[77] Children of parents who received high-quality recommendations aligned with these guidelines are more likely to initiate and complete the HPV vaccine series than those of parents who received a low-quality or no recommendation.[77] **The Panel Chair urges health care providers to strongly recommend HPV vaccination for all eligible adolescents.** Recommendations are most likely to be effective if providers:

- *Use announcement language*. Brief statements that assume parents are ready to vaccinate are associated with higher vaccine uptake than are open-ended, conversational approaches.[84-87] Announcements may be particularly effective for parents who are ambivalent or uncertain about HPV vaccination because these types of statements present vaccination as the social norm and affirm the provider's confidence in safety and effectiveness of the vaccine.[75] Open-ended discussions should be reserved for instances in which parents raise specific questions or concerns.

- *Bundle with other adolescent vaccines*. The HPV vaccine should be recommended at the same time and in the same way as other recommended adolescent vaccines, with HPV cancer prevention in the middle of the list (your son/daughter is due for vaccinations to help protect him/her from meningitis, HPV cancers, and whooping cough).[62,88]

- *Focus on vaccination of young adolescents*. Although ACIP recommends routine HPV vaccination of 11- and 12-year-olds, providers are more likely to recommend the vaccine strongly to older adolescents.[77] Providers should strongly recommend same-day HPV vaccination for all of their 11- and 12-year-old patients unless it is contraindicated. If parents suggest delaying vaccination, providers should emphasize that the vaccine is most effective when administered *well before* HPV exposure.[89] Additionally, younger adolescents exhibit strong immune responses following vaccination,[90] and those who initiate the series before 15 years of age require only two doses instead of three. Providers also should recommend the vaccine to older adolescents and young adults who have not completed the recommended series.

- *Promote vaccination of boys and girls equally*. Providers are less likely to consistently and strongly recommend HPV vaccination of boys than of girls,[77-79] and parents of boys are more likely than those of girls to cite lack of provider recommendation as a reason for nonvaccination.[80,81] Providers should deliver strong recommendations for both girls *and* boys to ensure that recent increases in vaccine coverage among boys continue. Males account for a growing proportion of HPV cancers in the United States due to the increasing incidence of HPV-associated oropharyngeal cancers.[16,91,92]

- *Repeat recommendations as needed.* Some parents respond to a provider's recommendation with hesitance or refusal. Many of these parents will decide to vaccinate their children at the same visit if providers persist in identifying and addressing parents' questions and concerns, reemphasize the importance of the vaccine, and restate the recommendation.[93] Furthermore, a significant proportion of parents who initially decline HPV vaccination will accept it at a future visit. One study found that provider recommendations, particularly high-quality recommendations, played an important role in subsequent vaccine acceptance.[94]

CDC and health professional organizations (e.g., AAP, AAFP) should continue to promote strong, clear provider recommendations for HPV vaccination. CDC should continue to develop and provide resources to support providers. Studies have found that providers in rural areas are less likely to recommend the vaccine,[95,96] and family physicians are somewhat less likely than pediatricians to consistently and strongly recommend the HPV vaccine.[78,79,97] Increasing the quality of recommendations delivered in rural settings, which are commonly served by family practice physicians,[98] may increase low vaccination rates observed in many rural areas. Continued monitoring also is needed to ensure that vaccine financing issues (e.g., provider concerns about upfront costs of the vaccine, inadequate reimbursement) do not interfere with access to the HPV vaccine or create disincentives for strong provider recommendations.

Systems-Level Efforts Facilitate Vaccination

Systems-level policies and practices have potential to drive substantial, enduring improvements in HPV vaccination rates by minimizing missed clinical opportunities, facilitating vaccine access, and promoting acceptance and normalization of the vaccine. Clinical practices, healthcare systems, and public health departments should identify and adopt strategies to increase their HPV vaccination rates. Programs that implement multiple strategies are more likely to be successful.[70] Analyses of successful programs and experiences with other vaccines and cancer prevention and screening recommendations have identified several evidence-based approaches to promote HPV vaccination, including:[70,71,75,97,99-109]

- *Conduct training.* Providers should be trained to deliver strong recommendations and address common parent questions and concerns, including those about safety.

- *Engage all office staff in vaccination efforts.* All office staff who interface with patients should be trained to ensure consistent, positive messaging about the vaccine. A vaccine champion and quality improvement team can foster a provaccination culture and promote positive change.

- *Use a tracking system.* It is critical to reliably identify patients due or overdue for vaccination and monitor vaccination rates. Tracking systems can be embedded within or integrated with electronic health records (EHRs). Integration with state immunization information systems (IIS) would enhance tracking capacity.

- *Prompt healthcare providers.* Clinicians should be informed when a patient is due or overdue for HPV vaccination. Prompts can be automatically generated by EHR systems or manually noted based on review of patients' charts prior to their appointments.

- *Implement standing orders.* Standing orders, which allow nurses or other medical personnel to administer vaccines using an established protocol without a direct order from a physician, increase vaccination rates in many settings.

- *Send reminders.* Parents should be informed when their children are due for a vaccine dose. One or more effective reminder methods can be used (e.g., phone, letter, email, text, EHR-based message), an approach that can be especially effective when handled in a centralized way.

- *Facilitate access.* Providing walk-in or immunization-only appointments can make it easier for patients

Quality Improvement Initiative Improves HPV Vaccine Initiation and Completion

The American Cancer Society's HPV Vaccinate Adolescents Against Cancers (VACs) program partners with primary care practices, health plans, hospital systems, and state entities to strengthen regional HPV vaccination efforts. Quality improvement (QI) partnerships are a core focus of the program. In 2017, VACs staff engaged Federally Qualified Health Centers (FQHCs) in evidence-based QI interventions, including an intensive learning collaborative that awarded Maintenance of Certification and Continuing Medical Education credits. About 40 participating FQHCs, comprising 119 clinic sites, increased their HPV vaccine series initiation rates by an average of 16 percentage points. Series completion rates rose by 18 percentage points, on average.

Source: American Cancer Society. HPV Vaccinate Adolescents Against Cancers: activity and impact report, 2017-2018. Atlanta (GA): ACS; 2018. Available from: https://www.mysocietysource.org/sites/HPV/ResourcesandEducation/CDC%20Annual%20Report%20%20Test/2018/VACs%202017-2018%20Activity%20and%20Impact%20Report.pdf

to receive the vaccine, particularly second or third doses. The vaccine should be offered opportunistically at all types of appointments unless contraindicated (e.g., well child, sick child, sports physicals).

- *Implement quality improvement initiatives.* Provider-, clinic-, and systems-level vaccination rates should be monitored and shared to provide accountability and incentivize improvement. Education and quality improvement programs focused on HPV vaccination could be implemented to meet requirements for board certification (i.e., Maintenance of Certification; see *Quality Improvement Initiative Improves HPV Vaccine Initiation and Completion* above).

The Panel Chair urges health system leaders to make HPV vaccination a high, measurable priority. Implementation of systems changes within large health systems could facilitate HPV vaccination of large numbers of adolescents and potentially increase overall vaccine coverage rates within geographic regions served. Some health systems already have established systems-level processes to support HPV vaccination, resulting in coverage rates well above the national average (see *Rapid Adoption of the HPV Vaccine within a Health System* on page 15).[97,99] Clinics and health systems should use resources shown to be effective in increasing HPV vaccination. These include resources developed by organizations such as the CDC,[63,110] AAP,[69] the American Cancer Society,[88] and the National HPV Vaccination Roundtable.[111,112] Advocacy organizations, health professional organizations, state vaccine coalitions, National Cancer Institute-designated cancer centers, and state health officials should engage health systems within their regions to encourage prioritization of HPV vaccination and implementation of practices and policies to increase coverage rates.

The updated HEDIS measure for adolescent vaccines promotes bundling of HPV with other recommended vaccines.

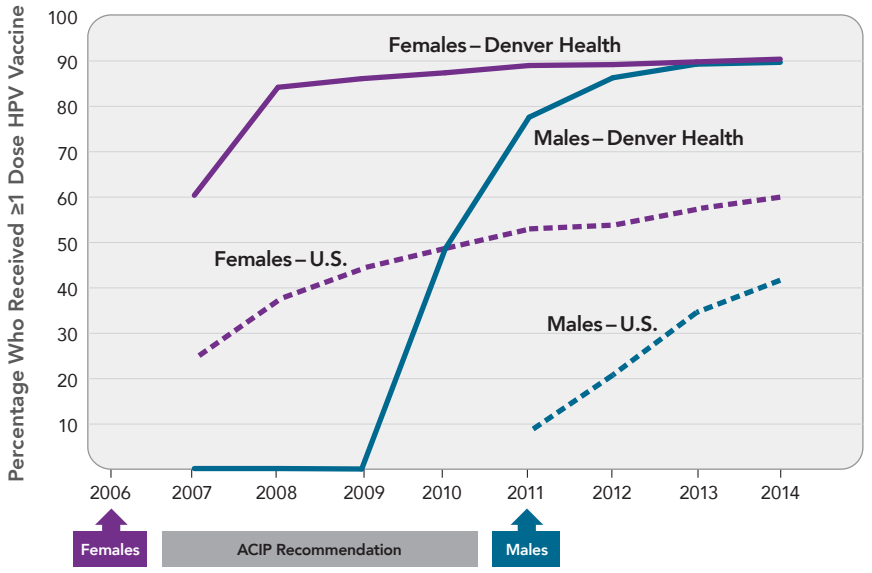
Clinics and healthcare systems are motivated by quality metrics established by external bodies. Healthcare Effectiveness Data and Information Set (HEDIS) quality measures are used as the basis of health plan accreditation by the National Committee for Quality Assurance and are used by health plans themselves to drive improvements in quality of care and services.[113] The updated measure for adolescent immunizations in HEDIS 2017 assesses the proportion of all adolescents

The* Healthy People 2020 *goal for HPV vaccines now includes both girls* and *boys.

who receive all recommended vaccines (meningococcal, Tdap, HPV) by their thirteenth birthdays.[114] This should provide incentives for providers and healthcare systems to bundle their recommendations for all adolescent vaccines and may help raise HPV vaccine coverage to the level of the other vaccines. The 2014 addition of a *Healthy People 2020* goal focused on males may encourage gender-neutral vaccination.[50] The Panel Chair agrees with the National Vaccine Advisory Committee that the Health Resources and Services Administration (HRSA) should include a measure for HPV vaccination of adolescents in the Uniform Data System, the required reporting system for HRSA grantees in community health centers, migrant health centers, health centers for homeless grantees, and public housing primary care organizations.[4]

Rapid Adoption of the HPV Vaccine within a Health System

Denver Health, an integrated urban safety net health system that serves more than 17,000 adolescents each year, has implemented several processes to facilitate vaccine uptake. The internally developed immunization registry (VaxTrax) creates a list of vaccines for which each patient is due. Vaccines are offered at every visit (even if they were previously declined), and providers are encouraged to bundle all adolescent vaccines together when recommending them. Standing orders allow adolescent vaccines, including the HPV vaccine, to be administered by a medical assistant. These processes contributed to rapid uptake of the HPV vaccine within Denver Health clinics. By 2014, nearly 90 percent of girls and boys (ages 13-17) had received at least one dose of the HPV vaccine. In contrast, national rates for 13- to 17-year-old girls and boys in 2014 were 60 percent and 42 percent, respectively.



Sources: Farmar AM, Love-Osborne K, Chichester K, et al. Achieving high adolescent HPV vaccination coverage. Pediatrics. 2016;138(5); Walker TY, Elam-Evans LD, Yankey D, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13-17 years—United States, 2017. MMWR Morb Mortal Wkly Rep. 2018;67(33):909-17.

Goal 2

Increase Parents' Acceptance of HPV Vaccination.

Parents and legal guardians are the primary decision makers about adolescent vaccination, particularly at the recommended ages for routine vaccination (11 to 12 years old).[115] HPV vaccination increasingly is a standard part of care for U.S. adolescents. The majority of parents have their children vaccinated against HPV. In 2017, more than 65 percent of 13- to 17-year-old adolescents had received at least one dose of the HPV vaccine.[7] Surveys of parents of unvaccinated teens indicate that a growing proportion are accepting of their children receiving the vaccine,[81] and many parents who initially decline the vaccine eventually accept it.[94]

This progress is likely due, in part, to communication campaigns—such as those carried out by the CDC,[116] ACS,[117] and Merck & Co.[118]—and promotion of the vaccine by a growing number of healthcare providers. However, more must be done to increase acceptance of the HPV vaccine. A 2015 survey found that about half of parents of unvaccinated teens did not intend to have their children vaccinated against HPV.[81] No single reason predominated, but common reasons cited by parents included:[80,81]

- Vaccination not needed
- Vaccination not recommended by healthcare provider
- Lack of knowledge about the vaccine or diseases caused by HPV
- Concerns about safety and side effects
- Son or daughter not sexually active

The Panel Chair encourages CDC, ACS, and other trusted organizations to continue to develop and deploy evidence-based communication campaigns to increase parents' acceptance of HPV vaccination. It is important that parents have access to clear, accurate information about HPV vaccination, particularly if they have questions or concerns. Key messages may include:

- The HPV vaccine prevents six cancers and other diseases.
- The HPV vaccine prevents cancers and other diseases in both girls and boys.
- The HPV vaccine is safe.
- The HPV vaccine is most effective when administered to young adolescents, well before they are exposed to HPV.

Campaigns should build on current knowledge and use existing materials whenever possible. Use of multiple tools and modes of communication will reach as many parents as possible. Strategies are needed to directly reach older adolescents and young adults who may make their own decisions about vaccination. Targeted campaigns may be needed in some cases to counteract widely circulated misinformation (see *Addressing Misinformation* on page 17).

While communication campaigns play an important role in multipronged approaches to increase HPV vaccine uptake, evidence suggests that interventions designed to influence parents' knowledge, thoughts, and feelings are likely to only modestly affect vaccination rates and may be most effective when a vaccine is new.[75,103] Ensuring that providers make strong recommendations and address parents' questions and concerns likely will be the most effective way to increase parents' acceptance of HPV vaccination and boost vaccine uptake (see Goal 1). Systems- and community-level interventions also may facilitate access to the vaccine so that parents with positive or neutral views of HPV vaccination have their children initiate and complete the series (see Goal 1 and Goal 3).

Addressing Misinformation

Misinformation about the HPV vaccine can be spread widely and quickly through social media and traditional media outlets, often with dire effects. Widespread dissemination of misinformation about safety has resulted in dramatic decreases in HPV vaccination in several countries, including Japan, Ireland, Colombia, Denmark, Romania, and India, leaving thousands of young people vulnerable to HPV cancers. In some cases, vaccination programs have even been terminated. Effective communication campaigns before and during vaccine rollout may make the general public less susceptible to misinformation. Effective crisis communication and leadership by policymakers are essential to prevent misinformation from having dramatic negative effects on coverage.

Once misinformation about vaccines takes hold, it can be exceedingly difficult to debunk. Contrasting myths with facts is often ineffective, and, in some cases, even reinforces false beliefs. There have been some success stories. Multipronged campaigns in both Ireland and Denmark have begun to reverse dramatic drops in HPV vaccine coverage precipitated by spread of misinformation about safety through the media. In both countries, coverage fell from around 90 percent to 50 percent or less. Both campaigns have involved multiple stakeholders, including policymakers, and have disseminated accurate information through multiple outlets. More research is needed to better understand how and why misinformation spreads, examine the role of media and policymakers in fostering or halting HPV vaccine coverage collapse, and develop better ways to effectively combat it.

Strategies that have been recommended to help overcome misinformation include:

- Keep key messages simple.
- Emphasize core facts, not the myth.
- Give explicit warnings before mentioning a myth.
- Provide an alternative explanation to fill gaps left by debunking the myth.
- Emphasize scientific consensus about the benefits of HPV vaccination.
- Use visuals to convey core facts whenever possible.

Stakeholders, including national and local governments, advocacy groups, and others, should monitor the emergence of messages with potential to undermine confidence in the vaccine and quickly mobilize tailored responses. It is rarely possible to change the minds of people who strongly oppose vaccination; rather, the goal should be to provide the general public with accurate information from credible sources to make them more resilient to unsubstantiated anti-vaccine statements and stories.

Sources: Corcoran B, Clarke A, Barrett T. Rapid response to HPV vaccination crisis in Ireland. Lancet. 2018;391(10135):2103; Cordoba V, Tovar-Aguirre OL, Franco S, et al. Barriers and facilitators of human papillomavirus (HPV) vaccination during the implementation of the school-based HPV vaccine program in Manizales, Colombia [poster]. Presented at: ASCO Annual Meeting; 2018; Chicago, IL: Journal of Global Oncology. Available from: http://ascopubs.org/doi/abs/10.1200/jgo.18.11000; World Health Organization. Denmark campaign rebuilds confidence in HPV vaccination [Internet]. Geneva (CH): WHO; 2018 Feb [cited 2018 Aug 28]. Available from: http://www.who.int/features/2018/hpv-vaccination-denmark/en/; Penta MA, Baban A. Mass media coverage of HPV vaccination in Romania: a content analysis. Health Educ Res. 2014;29(6):977-92; Sabeena S, Bhat PV, Kamath V, Arunkumar G. Global human papilloma virus vaccine implementation: an update. J Obstet Gynaecol Res. 2018;44(6):989-97; Pluviano S, Watt C, Della Sala S. Misinformation lingers in memory: failure of three pro-vaccination strategies. PLoS One. 2017;12(7):e0181640; World Health Organization Regional Office for Europe. Best practice guidance: how to respond to vocal vaccine deniers in public. Copenhagen (DK): WHO Regional Office for Europe; 2017. Available from: http://www.euro.who.int/__data/assets/pdf_file/0005/315761/Best-practice-guidance-respond-vocal-vaccine-deniers-public.pdf; Cook J, Lewandowsky S. The debunking handbook (version 2). St. Lucia (AT): University of Queensland; 2012 Jan. Available from: https://www.skepticalscience.com/docs/Debunking_Handbook.pdf

Research Priority: Harnessing Social Media

Social media use has grown dramatically over the past decade. Research is needed to identify ways to effectively use social media to spread research-tested messages about HPV and HPV vaccination.

Goal 3

Maximize Access to HPV Vaccination Services.

Ensuring that HPV vaccination is affordable and convenient for all U.S. adolescents will support optimal vaccine uptake. Access barriers likely play a role in low and uneven HPV vaccine uptake in the United States. These barriers—and approaches for addressing them—may differ across geographic regions, populations, and clinical settings. National, regional, and local efforts are needed to understand and address existing and potential barriers to access.

Coverage for HPV Vaccination Costs Must Be Maintained

The HPV vaccine is among the most expensive vaccines in the United States,[119] but multiple sources of private and public financing ensure that the cost of the vaccine is covered for nearly all age-eligible adolescents.[120] The Affordable Care Act requires private insurance plans and marketplace plans to cover all ACIP-recommended immunizations, including the HPV vaccine, with no consumer cost sharing.[121] The vaccine also is available through the Vaccines for Children (VFC) Program for children under age 19 who are Medicaid-eligible, uninsured, underinsured, or American Indian/Alaska Native. HPV vaccine costs also are covered by Medicaid, state Children's Health Insurance Programs, and Merck-sponsored patient assistance programs.[120] **The Panel Chair asserts that insurance coverage for preventive services must be maintained to ensure that cost does not limit U.S. adolescents' access to HPV vaccination**.

Alternative Settings May Expand Access to HPV Vaccination in Some Situations

Ideally, all adolescents would receive regular care—including immunizations—from a provider with

whom they have an ongoing relationship. However, many adolescents do not receive regular preventive care through medical homes.[122] In its 2012-2013 report, the Panel recommended that, for those adolescents, HPV vaccination be promoted and facilitated in venues outside the medical home, citing pharmacies and schools as potential sites within the "medical neighborhood" that could increase access to HPV vaccination. Since that time, these venues have been explored by various groups in different settings, and a clearer picture of the associated challenges and opportunities has emerged.

Both pharmacies and schools have potential to provide convenient access to HPV vaccination. Nearly 90 percent of U.S. residents live within five miles of a community pharmacy;[123] pharmacies often have longer operating hours and shorter wait times than doctors' offices and many provide walk-in vaccinations. Schools also provide the opportunity to reach the vast majority of adolescents, and school-based HPV vaccination programs have been highly successful in many countries around the world.[34] In the United States, pharmacies and schools have not played major roles in HPV vaccination to date due to several challenges (see *Challenges Associated with HPV Vaccination in Pharmacies and Schools* on page 20).

Given these challenges, it is unlikely that HPV vaccination in pharmacies or schools will contribute to substantial increases in national HPV vaccination rates in the near future. However, alternative settings may expand access in some situations. Offering and promoting HPV vaccination in schools, pharmacies, and other sites within the medical neighborhood may be particularly useful in rural areas, which have fewer primary care physicians per capita than urban areas and greater obstacles to access.[124] School-located programs have helped increase coverage rates in some areas (see *School Program Increases HPV Vaccination in Rural North Dakota* on page 21).[125,126] The small but growing number of school-based health centers—which provide comprehensive healthcare services, have dedicated staff, and often serve large numbers of VFC-eligible students—may be able to more easily overcome the most common barriers to school-located vaccination.[126,127]

State and local laws, local cultural factors, potential partner organizations, and available resources should be considered when exploring options to increase access to HPV vaccination. Providers and programs in alternative settings should communicate and coordinate with primary care providers to the extent possible, including reporting all administered vaccine doses to the state's immunization information system (IIS). The Panel Chair supports the call by the National Vaccine Advisory Committee[4] for greater investment and commitment to promote interoperability of electronic health record systems and IIS. Once interoperability is achieved, states should consider requiring providers to report vaccinations to IIS to ensure that all vaccine providers have access to complete, timely information.

Challenges Associated with HPV Vaccination in U.S. Pharmacies and Schools

Pharmacies

- *Restricted authority in some states*—Pharmacists in 48 states and the District of Columbia have authority to administer the HPV vaccine, but 11 of these states do not allow HPV vaccination of 11- and 12-year-old children and several other states require a physician prescription or protocol.

- *Inadequate insurance coverage*—Many private insurance plans do not cover or provide inadequate coverage for vaccine administration within pharmacies. Relatively few pharmacists are VFC providers. Some states do not enroll pharmacies in VFC, while pharmacies in other states may elect not to participate in the program due to the cumbersome requirements.

- *Low demand*—Pharmacists who stock the HPV vaccine report providing very few doses, and parents consider doctors' offices to be a better environment than pharmacies for adolescent vaccination.

Schools

- *Complicated billing*—Students within a school or school district may be covered by a range of private insurance plans and public programs, which makes billing cumbersome and costly.

- *Competing priorities*—Schools have limited resources and must focus these resources on education and other priorities (e.g., transporting students, meals).

- *Low demand*—Surveys of parents suggest support for school-located vaccination, but most say they prefer their adolescents to be vaccinated in providers' offices. Participation in school-located HPV vaccination programs to date has generally been low in the United States.

Sources: Islam JY, Gruber JF, Lockhart A, et al. Opportunities and challenges of adolescent and adult vaccination administration within pharmacies in the United States. Biomed Inform Insights. 2017;9:1178222617692538; Barden S. National HPV Vaccination Roundtable Pharmacy-located HPV Vaccination Pilot Project: final report. Lansing (MI): Michigan Pharmacists Association; 2018. Available from: http://hpvroundtable.org/wp-content/uploads/2018/02/Pharmacy-located-HPV-Vaccination-Pilot-Final-Report_MI.pdf; Curry S, Vanderpool R, Lopez K, et al. National HPV Vaccination Roundtable Pharmacy-Located HPV Vaccination Pilot Project: final report. Carrboro (NC): Cancer Prevention and Control Research Network; n.d. Available from: http://hpvroundtable.org/wp-content/uploads/2018/02/CPCRN_Pharmacy-located-HPV-Vaccination_Pilot-Project-Findings-from-IA_KY_OR.pdf; Hastings TJ, Hohmann LA, McFarland SJ, et al. Pharmacists' attitudes and perceived barriers to human papillomavirus (HPV) vaccination services. Pharmacy (Basel). 2017;5(3); Shah PD, Marciniak MW, Golden SD, et al. Pharmacies versus doctors' offices for adolescent vaccination. Vaccine. 2018;36(24):3453-9; American Pharmacists Association. Pharmacist authority to immunize by type of immunization [Internet]. Washington (DC): APhA; [updated 2018 Jan 18; cited 2018 Jun 28]. Available from: https://www.pharmacist.com/immunization-center; Daley MF, Kempe A, Pyrzanowski J, et al. School-located vaccination of adolescents with insurance billing: cost, reimbursement, and vaccination outcomes. J Adolesc Health. 2014;54(3):282-8; Kempe A, Allison MA, Daley MF. Can school-located vaccination have a major impact on human papillomavirus vaccination rates in the United States? Acad Pediatr. 2018;18(2S):S101-S5.

School Program Increases HPV Vaccination in Rural North Dakota

Access to healthcare is limited in many rural counties in North Dakota. In 2012, some of these counties had rates of HPV vaccine series completion as low as 10 percent. To address this, the North Dakota cancer control and state immunization programs partnered with local public health units, schools, and communities to implement an in-school vaccination program. Vaccinations were provided during school hours in 20 middle and high schools in 4 counties. Parents provided information on insurance coverage and Vaccines for Children Program eligibility. Public health units billed insurance companies, Medicaid, or parents, as appropriate, to cover vaccine costs and administration fees. In one participating county, coverage rates increased by 18 percent within two years, and the program became self-sustaining in three years. The success of this program was attributed to the strong collaborative efforts of the North Dakota state immunization and comprehensive cancer control programs to inform parents of the need for the vaccine and increase access to it.

Sources: Pastir J. School HPV immunization clinics increase vaccination rates in North Dakota. Atlanta (GA): Centers for Disease Control and Prevention; 2017 Nov 30. Available from: https://nccd.cdc.gov/nccdsuccessstories/showdoc.aspx?s=14291&dt=0; Personal communication with Janna Pastir (Comprehensive Cancer Prevention and Control Program, North Dakota Department of Health, Bismarck, ND) and Molly Howell (Division of Disease Control, North Dakota Department of Health, Bismarck, ND). 2018 Aug.

Goal 4

Promote Global HPV Vaccine Uptake.

HPV was responsible for nearly 630,000 cases of cancer worldwide in 2012, the most recent year for which data are available (Figure 5). Although HPV causes multiple cancers, the vast majority of HPV cancers worldwide—530,000—are cervical cancers. Most HPV cancers could be prevented by currently available HPV vaccines.[19] The potential impact of HPV vaccination is greatest in less developed countries.

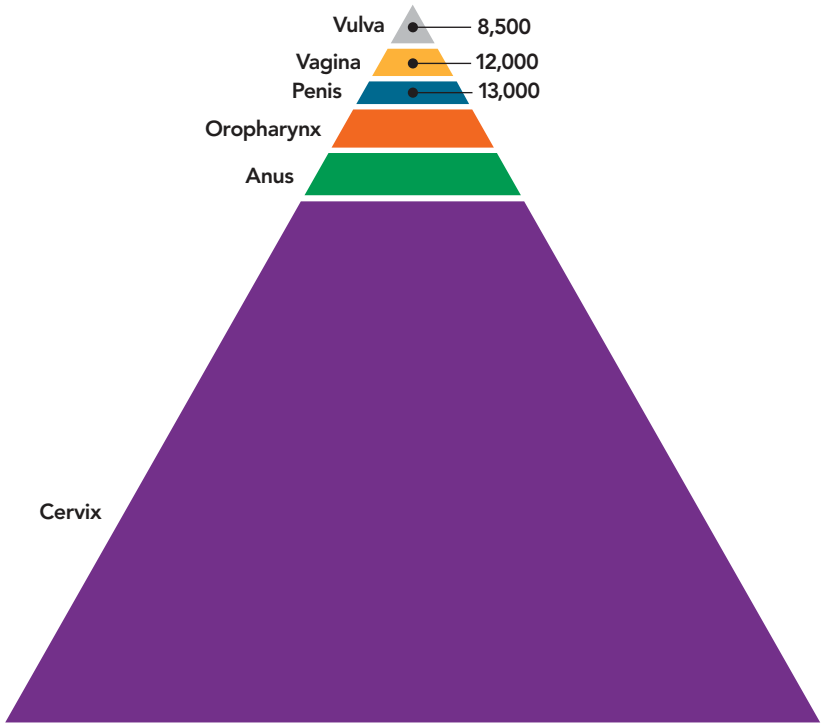
HPV Vaccination Is Low in Countries with Most Cervical Cancer Cases and Deaths

The vast majority of cervical cancer cases and deaths occur in countries with lower levels of socioeconomic development.[128] The number of cervical cancer deaths in less developed regions is predicted to increase by about 50 percent by 2030.[129] Vaccination rates in less developed regions are disproportionately low. In 2014, it was estimated that fewer than 3 percent of 10- to 20-year-old girls in less developed regions had completed the HPV vaccine series, compared with 34 percent of girls in more developed regions.[130] Despite the World Health Organization (WHO) recommendation that all countries vaccinate 9- to 14-year-old girls,[24] as of May 2018, only 9 low- and lower-middle-income countries (LLMICs) had included the HPV vaccine in their national vaccination programs, compared with 70 high- and upper-middle-income countries.[131]

In 2014, it was estimated that fewer than 3 percent of 10- to 20-year-old girls in less developed regions had completed the HPV vaccine series.

The disproportionate numbers of cervical cancer cases and deaths in less developed regions are due to the challenges of implementing cervical cancer screening programs, which have substantially reduced cervical cancer in many high-income countries, including the United States.[132,133] While increasing HPV vaccination of adolescents will prevent future cancers in less

Figure 5. Cancers Caused by HPV Worldwide



Source: de Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. Int J Cancer. 2017;141(4):664-70; Note: de Martel et al. include cancers of the oral cavity and larynx in their estimate of HPV-attributable cancers. The U.S. Centers for Disease Control and Prevention has concluded that HPV causes some cancers of the oropharynx, but that the evidence that HPV causes cancers of the oral cavity and larynx is insufficient. Thus, numbers in this figure include estimates for oropharyngeal but not oral cavity and laryngeal cancers.

developed regions, development and deployment of cost-effective screening programs are needed to alleviate the burden of cervical cancers among the current generation of women.[134-136]

HPV Vaccination Is Feasible in Low-Resource Settings

HPV vaccination in low- and middle-income countries has been supported by many organizations, including pharmaceutical companies; charitable organizations; PATH; the Pan American Health Organization (PAHO) Revolving Fund; and Gavi, the Vaccine Alliance.[137] These organizations have supported small-scale demonstration projects, as well as national introductions of the HPV vaccine. Since 2013, most financial support for HPV vaccination programs in LLMICs has come from Gavi, an international public-private partnership focused on increasing access to immunization in lower-income countries.

Although the pace of vaccine introduction has been slower than hoped in low-resource settings, there are reasons to be encouraged. At least 45 low- and middle-income countries have gained experience with HPV vaccination through demonstration projects or national programs. These experiences have yielded important lessons and identified several factors that contribute to program success (see *HPV Vaccination in Low- and Middle-Income Countries: Lessons Learned* on page 23).

National programs and demonstration projects in LLMICs have been highly effective. Among 34 LLMICs with coverage data, nearly half delivered at least one

dose to more than 90 percent of the target population of girls, and all of these programs achieved at least 60 percent coverage with at least one dose.[138] In addition to being effective, these programs illustrate that many countries have the political will and recognition of the need to introduce the vaccine.

U.S. Support Is Needed to Promote Global HPV Vaccination

Many organizations—including WHO, PAHO, Gavi, and others—have increased access to HPV vaccines in many low-resource areas over the past ten years, and the United States has contributed to these efforts. **The Panel Chair urges the United States to continue to support implementation and sustainability of HPV vaccination programs around the world, particularly in low- and middle-income countries**.

Gavi remains the best mechanism for promotion of HPV vaccination in LLMICs. The United States—which contributed $275 million to Gavi in 2017[139]—should continue its financial support of this partnership.

HPV Vaccination in Low- and Middle-Income Countries: Lessons Learned

Coordination and Planning

- Planning processes should include representatives from the ministries of health, education, and finance and other key experts.
- National immunization program involvement is critical for effective vaccine delivery.
- Proactive development of crisis communication plans will help address safety scares.

Communication and Education

- Social mobilization in communities should be initiated well in advance of vaccination campaigns.
- Messaging should focus on cervical cancer prevention; safety and efficacy, including lack of fertility impact and long-term adverse events; government endorsement; and vaccination logistics.

Delivery

- School-located delivery should be pursued if school attendance is high and resources allow. If school enrollment is low, a mixture of strategies may help attain good coverage. Out-of-school girls should have the opportunity to receive the vaccine.

Integration

- Once the first round of vaccination is complete, HPV vaccination should be gradually integrated into existing structures and processes for delivery of other vaccines.

Sources: Gallagher KE, Howard N, Kabakama S, et al. Lessons learnt from human papillomavirus (HPV) vaccination in 45 low- and middle-income countries. PLoS One. 2017;12(6):e0177773; World Health Organization. HPV vaccine communication: special considerations for a unique vaccine: 2016 update. Geneva (CH): WHO; 2016. Available from: http://apps.who.int/iris/bitstream/handle/10665/250279/WHO-IVB-16.02-eng.pdf

U.S. agencies, including CDC and NCI, should continue working with other global health partners to promote HPV vaccination. Examples of valuable support include providing input on HPV vaccine-related policies and guidelines; offering technical and field support; and contributing to implementation research, such as research on the costs of national HPV vaccination programs.[140,141] CDC and NCI also should continue to support cancer control planning and tumor registry activities in less developed regions. This will help countries gather the resources and data needed to make decisions about and measure effectiveness of HPV vaccination programs. The U.S. President's Emergency Plan for AIDS Relief (PEPFAR) should promote HPV vaccination as part of its efforts to address the cervical cancer burden in HIV-infected women, including through the Partnership to End AIDS and Cervical Cancer.[142]

The United States also can promote HPV vaccine uptake in less developed regions by funding research on ways to make vaccine distribution, storage, and administration easier and less expensive. In particular, additional evidence is needed on the efficacy and duration of protection provided by a single dose of the HPV vaccine. The shift to a two-dose schedule decreased the logistical challenges and costs of HPV vaccination. Delivery of one dose would be even easier and less costly, facilitating introduction and sustainability of HPV vaccination programs around the world.[143,144] NCI and the Bill & Melinda Gates Foundation recently launched a clinical trial that will determine whether a single dose of the HPV vaccine works as well as two doses in young women.[145] Results should be available in 2024. These types of trials should be supported to ensure that the benefits of HPV vaccination are provided with optimal cost-effectiveness.

Research Priority: Test Effectiveness of One Dose

Additional evidence is needed on the efficacy and duration of protection of a single HPV vaccine dose. If one dose were sufficient, vaccination program costs could be considerably lower, which may lead to more widespread uptake worldwide.

CONCLUSIONS

HPV causes nearly 630,000 cancers worldwide each year, including nearly 34,000 in the United States. The majority of these cancers could be prevented by HPV vaccination. In its 2012-2013 report, the President's Cancer Panel found that underuse of HPV vaccines was a serious but correctable threat to progress against cancer and identified several goals to increase uptake.

There has been very encouraging progress in HPV vaccine uptake in the United States and globally over the last five years. However, HPV vaccination rates are still too low to achieve the full potential for cancer prevention. As of 2017, less than half of U.S. adolescents were fully vaccinated. In addition, HPV vaccines are not included in the national vaccine programs of many low- and middle-income countries, where the vast majority of cervical cancer cases and deaths occur. In this report, the Panel Chair identifies strategies for building on recent progress and overcoming persistent barriers to vaccine uptake. While local cultural factors and available resources should inform efforts to increase HPV vaccination, knowledge and experience suggest that the following priorities likely will have the greatest population-level impact.

Provider- and systems-level changes hold the greatest potential to increase U.S. HPV vaccination rates. Provider recommendation is one of the strongest predictors of adolescent HPV vaccine uptake, but some providers give weak or unclear recommendations. Providers should clearly and strongly recommend same-day vaccination of all eligible adolescents. Systems-level changes that prioritize HPV vaccination and provide easy access to the vaccine also would reduce missed clinical opportunities to recommend and administer the HPV vaccine. Such interventions would contribute strongly to increasing HPV vaccine coverage to the same levels as for other adolescent vaccines.

Partnerships and collaborations are essential. Diverse groups of stakeholders—including cancer control and immunization experts and organizations, health professional organizations, government agencies, advocacy organizations, and others—have partnered to overcome barriers to HPV vaccination. These partnerships have been key to many of the successes achieved over the past few years. Stakeholders should continue to engage in and support collaborations to accelerate progress in HPV vaccine uptake.

Progress and momentum built over the past half decade have created a compelling opportunity to increase HPV vaccine uptake further and dramatically reduce—and perhaps eventually largely eliminate—the preventable burden of HPV cancers. The elements of success are at hand: evidence of the benefits of HPV vaccination is strong and growing, numerous stakeholders are committed to the cause, and the knowledge and tools to increase vaccination coverage are available. Now is the time to apply what is known to ensure that today's young people and future generations are protected against HPV cancers. Cancer and immunization stakeholders worldwide must renew their collective commitment to achieving HPV vaccination targets. All should rally without hesitation around the ultimate goal of cancer prevention.

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APPENDIX: ACRONYMS

ACRONYM	DEFINITION
AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
ACS	American Cancer Society
AIDS	Acquired immunodeficiency syndrome
CDC	Centers for Disease Control and Prevention
EHR	Electronic health record
FDA	Food and Drug Administration
HEDIS	Healthcare Effectiveness Data and Information Set
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HRSA	Health Resources and Services Administration
NCI	National Cancer Institute
NHANES	National Health and Nutrition Examination Survey
PAHO	Pan American Health Organization
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
QI	Quality improvement
VFC	Vaccines for Children
WHO	World Health Organization

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