Human Papillomavirus Vaccine

The Cancer Prevention Moonshot

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KEYWORDS

• HPV vaccine • Vaccine equity • Cervical cancer • HPV virus • Oncogenic virus

KEY POINTS

- Cervical cancer strikes more than 600,000 individuals with a cervix a year.
- The human papillomavirus (HPV) vaccine, when given at the 9 to 14 years recommended age range, can prevent 90% of cervical cancer.
- The HPV vaccine can also prevent most of the throat, anal, vulvar, and vaginal cancers when administered at the targeted age range.
- HPV vaccination remains underused in the United States as a robust cancer prevention tool.
- Global HPV vaccine supply is currently restricted, and many lower income and middle-income countries do not have access to this cancer prevention tool, despite having the highest burden of cervical cancer.

BACKGROUND

The approval of the HPV vaccine in 2006 ushered in an unprecedented era as a tool to prevent cervical cancer, in addition to other human papillomavirus (HPV)–caused malignancies. Given the public attention of the Cancer Moonshot efforts, here is a "moonshot" at our fingertips. In the case of the HPV vaccine, we claim both that the Moonshot has landed, but that for many, it remains a far away journey.

Burden of Disease

HPV is the most common sexually transmitted infection (STI) worldwide. It is a DNA virus causing mostly asymptomatic infections, with incidence peaking among those

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at younger ages, 90% of whom will clear the infection within 24 months without intervention.[1] There are more than 150 strains of the HPV virus, and persistence of replicating virus with a carcinogenic strain can lead to precancerous and cancerous lesions.[1,2] The time from initial infection with HPV to an invasive HPV-associated cancer in those with persistent disease is on average 15 to 20 years and dependent on HPV strain, individual immunological status, other coinfections, and tobacco use, among others.[2] The cancers associated with HPV include cervical, penile, vulvar, vaginal, anal, and oropharyngeal carcinoma.[1,2] In the United States approximately 37,000 new cases of HPV attributable cancers occur annually.[1] Although HPV infections can cause a variety of cancers, for this review the authors focus on cervical cancer, as it has the largest proportion of global morbidity and mortality of the HPV-associated cancers.[2] The authors use the terms "female," "women," and "girls" to describe genetic females with the understanding that not everyone with a cervix may identify as a female, woman, or girl.

Cervical cancer is the fourth most common cancer among females worldwide.[2] Globally, 91% of HPV-related cancers in females are cervical cancers, and most of the cases are attributable to infection with an oncogenic HPV strain[2]; these include HPV 16 (50% of cervical cancer cases); HPV 18 (20%); and HPV 31, 33, 45, 52, and 58 (19% combined).[2–4] In 2020, there were just more than 600,000 new cases of and 340,000 deaths from cervical cancer globally.[2] This HPV-associated cancer clearly has an immense impact—not just for those contracting the cancer—but also far beyond. When a woman dies, the impact on her children and those in her family is detrimental and life altering, not to mention the loss in our societal fabric.

An important distinction in the discussion of cervical cancer is that between the 2 major subtypes, adenocarcinoma and squamous cell carcinoma. Most of the cervical cancers (70%–75%) are squamous cell; adenocarcinoma is less common (25%). High-grade cervical dysplasia is a risk factor for both. Squamous cell cervical carcinoma is more commonly associated with HPV 16 (60%) than with HPV 18 (13%). Adenocarcinoma, on the other hand, is more commonly associated with HPV 18 (37%) than HPV 16 (36%). Although squamous cell carcinoma remains the most common cervical cancer type, adenocarcinoma is increasing in incidence, is less readily identified on routine PAP smear, develops at a younger age than squamous carcinoma, and may have a worse prognosis.[5,6]

In the United States, the incidence of not only adenocarcinoma but also stage IV cervical cancer at diagnosis is increasing. A recent study found a rate of increase in diagnosis of stage IV cervical cancer at diagnosis of 1.3% a year in the last 18 years, with a 2.9% increase in adenocarcinoma of the cervix; this is certainly alarming given the 5-year survival rate of 17%. This study also found that in the United States, black women have disproportionately high rates of stage IV cervical cancer at diagnosis (1.55 times the rate of white women). In addition, it found the population with the highest rate of increase to be young white women (ages 40–44 years) in the Southern United States, with a rate of increase of 4.5% a year. White women also have higher rates of absent guideline-based screening, and white teenagers have the lowest rates of HPV vaccination.[7] Inequities exist in the United States surrounding later stage diagnosis, increasing incidence, and guideline-based screening.

Difference in HPV infection and cervical cancer rates exist on a global scale as well. Although worldwide the prevalence of HPV infection among those with normal cytology is approximately 12%, in Sub-Saharan African it is 24%.[8–10] Eighty-four percent of cervical cancer cases worldwide are from resource-limited regions. Among females in these regions, cervical cancer is the second most common type of cancer and the third most common cause of cancer mortality. In Africa and Central America, it

is the leading cause of cancer-related mortality. The mortality rates also vary significantly with a rate of less than 2 per 100,000 in higher income countries compared with 28 per 100,000 in lower income countries, an 18-fold increase; this is due to a lack of widespread HPV vaccination, a lack of screening and treatment of cervical precancer, and absence of treatment options in many low-resource settings.[2,8,9]

Further, human immunodeficiency virus (HIV) infection intensifies HPV carcinogenesis. Females with HIV are at an increased risk of progression to high-grade dysplasia and subsequent cervical cancer.[10] Among females with HIV, there is 6 times the risk of cervical cancer. South and Eastern Africa are the most effected; in Eastern African nearly 27% of females with cervical cancer also live with HIV. In Southern Africa this number is nearly 64%.[11]

The Human Papillpmavirus Vaccine

HPV was found to be an oncogenic virus in the 1980s; after this discovery there was a relatively rapid production of a quadrivalent HPV vaccine first authorized for use in the United States in 2006 for HPV 6, 11, 16, and 18. Soon after, the bivalent vaccine was released in 2007 for HPV 16 and 18, followed by the nonavalent vaccine in 2014 covering the most HPV strains yet (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58).[2] The goal with each is to administer before onset of sexual activity and thus exposure to HPV for maximum efficacy.[1,2] All 3 vaccines use recombinant DNA technology, none contain live virus, and therefore they cannot transmit virus. HPV protection comes from neutralizing antibodies to the major HPV viral coat protein, L1. This purified structural L1 protein self-assembles to form HPV type–specific viral-like particles against high-risk HPV types included in the specific vaccine that are highly immunogenic. These vaccine-induced immunoglobulin G antibodies then reach the site of a natural HPV infection to neutralize virus.[2]

All of the HPV vaccines initially were approved with a 3-dose vaccination schedule. After evidence of noninferiority with a 2-dose vaccination schedule, this was approved for each vaccine in individuals 9 to 14 years of age.[2] The World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) released a statement in early 2022 stating that a single dose of the HPV vaccine garners similar protection to a 2-dose schedule.[12] Although this has not been adopted in the United States, it may in time as the evidence emerges. Currently in the United States, a 2-dose regimen (vaccination at 0, 6–12 months) is recommended for those who receive the first dose before the age of 15 years, and a 3-dose regimen (vaccination at 0, 1–2, and 6 months) is recommended for those who receive the first dose after the age of 15 or with immunocompromising conditions.[1]

With either dosing schedule, the HPV vaccine is highly efficacious. It has the potential to prevent 90% of HPV attributable cancers and is 99% efficacious against HPV 16 and 18 if administered before exposure.[1,10] The immune response to the vaccine is much higher than with natural infection. As the vaccine nears 2 decades on the market, there are now excellent longevity data, and it does not seem a booster is needed.[10] A single case of cervical cancer can be prevented by vaccinating 70 females. In addition, among HIV-positive patients seroconversion against HPV has reliably been observed underscoring the vaccines potential to alleviate disparities in HPV infection and subsequent cervical cancer.[2,10]

The current WHO recommendations are to prioritize HPV vaccination of females ages 9 to 14 years before the onset of sexually active, with the goal of reaching 90% full vaccination by age 15 years by the year 2030 to eliminate cervical cancer as a public health issue.[2,10] The most recent WHO position statement notes that gender-neutral vaccination globally is less cost-effective than focusing vaccination

efforts on girls and thus specifically prioritizes females.[2] In the United States, HPV vaccination is recommended for 11- to 12-year-old girls as well as 13- to 26-year-old girls who have not been vaccinated or did not complete the series with a similar goal of vaccination before initiation of sexual activity and exposure to HPV, although the vaccine can be given as early as age 9 years.[1] In addition, routine vaccination of 11- to 12-year-old boys or those aged 13 to 26 years not previously vaccinated or who have not received all recommended doses is recommended in the United States.[1] Some adults aged 27 to 45 years who are not fully vaccinated may benefit from the vaccine and can have individual decision-making discussions with their health care provider about the HPV vaccine.[1]

Human Papillomavirus Vaccine Uptake and Distribution

The HPV vaccine has the enormous potential to prevent cervical (and other) HPV-associated cancers. In the United States, the benefit of the availability of the HPV vaccine in terms of HPV infection rates is clear. In a recent analysis comparing HPV rates between females born in the 1980s and those born in the 1990s, HPV infection rates decreased from 12.5% to 5.6%, respectively. Even more encouraging, the rates of HPV 16 and 18 infection, the most oncogenic strains, decreased from 15.2% to 3.3% over the decade.[13] Since being approved in the United States in 2006, HPV vaccination coverage among adolescents has increased over time; as of 2021 nearly 77% of adolescents in the United States had received at least 1 dose, with 62% being up-to-date.[14] Yet despite estimates that initiation of HPV vaccination programs could, over the next 100 years, prevent 60 million cases of and 45 million deaths from cervical cancer, to date just 125 countries or 64% have initiated an HPV vaccine program within their national immunization program.[2] What has affected uptake and distribution of this life-saving vaccine on a global scale?

As previously mentioned, the WHO recommended the vaccine be given to all females ages 9 to 14 years in 2009. National vaccination campaigns, however, require money and infrastructure. The formal WHO recommendation did allow lower income countries to receive some funding and access to the vaccine through Gavi, an international public private aid organization. Gavi provides support to the 54 countries with the lowest annual gross domestic product and was able to secure a price of $4.55 for the HPV vaccine, significantly less expensive than the more than $100 it initially cost in the United States.[15] Yet, as of 2022, most of the Gavi-supported countries have yet to launch a national HPV program.[15] Further, most middle-income countries that do not qualify for Gavi funding, but that do not have the national public health funding for a new HPV national vaccination program, remain without HPV vaccine programs. The new evidence from SAGE that a single-dose regimen is acceptable is hoped to mitigate barriers around cost and resources bolstering national vaccination efforts.[12]

In the United States, despite being a wealthy nation with funds and infrastructure, the cancer-preventing HPV vaccine certainly was not met with immediate and rapid uptake. In the first year after the HPV vaccine was recommended in the United States, 25% of females received it. By 2015 63% had received at least 1 dose, and in 2021 77% of females (and 74% of males) had received 1 dose.[14,16] Although this has translated to decreasing HPV infections and has continued to increase with public health efforts, it is certainly not the 90% WHO benchmark. Reasons parents in the United States cite for choosing to not vaccinate their children include feeling the vaccine is not necessary, lack of provider recommendation, and not being a school requirement.[17] Sexual stigma around HPV as an STI has also been identified as a barrier.[18] Cost has also been cited as a reason; in the United States for those who qualify under

the age of 18 years the vaccination is paid for by Vaccines For Children, a federally funded income-based program through the CDC.[1] For those who do not quality for this assistance, the cost is just more than $250 for each dose, with the actual cost being insurance based and variable.[19]

Several HPV vaccine delivery models have been associated with rapid and high rates of uptake. Countries in high- and low-income settings that use school-based vaccination have achieved high coverage. In Australia, the national HPV vaccination program was initiated as a school-based program in 2007; this led to a national rate of 83% for vaccination initiation soon after and 70% for completion with increasing coverage in recent years. Such a program has been said to have a "normative influence" that is convenient for parents.[20] Similarly, in Rwanda starting in 2011 the 3-dose course was given free of charge to females in grade 6, with 93% coverage nationwide. This was after significant planning efforts centered on reaching females in and out of schools, partnering between the Ministry of Health and Education, and using community health workers. There were coordinated speeches by health-care professionals, clergy, and government officials including the First Lady promoting the HPV vaccine, and teachers were trained to discuss the vaccine with their students before the roll-out.[21]

In the United States, where school-based HPV vaccine is rarely used, high coverage has been achieved when delivering the HPV vaccine in a culturally accepted manner. One example is the Navajo Area Indian Health Service Unit in Chinle Arizona, which achieved a nearly 83% HPV vaccination rate among teenage girls (compared with 50% in Arizona among females age 13–17 years and 47% of American Indian and Alaska natives nationwide of the same age); this was accomplished by deliberate efforts by the Service unit to "weave HPV vaccination into Navajo culture by connecting it to coming-of-age ceremonies that observe transition into adulthood" and including traditional healers.[22] These efforts have been exceedingly effective and show that culturally appropriate planning, infrastructure, and support can lead to high HPV vaccination rates.

Cost-Effectiveness

The cost-effectiveness of the HPV vaccination has been well studied in the United States and globally. In the United States, the economic costs of HPV-related warts and cervical disease is estimated to be $4 billion annually.[23,24] In a 2008 analysis, a simplified incidence-based model was used to examine the health and economic effects of implementing HPV vaccination in 12-year-old girls. The study aimed to address the question, "What is the cost per QALY gained by adding vaccination of 12-year-old girls to existing cervical cancer screening practices in the United States?". The quality-adjusted life-year (QALY) is a generic health measure of disease burden. QALY attempts to combine the morbidity and mortality of a disease or health condition into a single number and estimate how many quality months or years a person may gain as a result of a particular treatment. The study examined HPV-related health outcomes including cervical cancer, cervical intraepithelial neoplasia (CIN) 1 to 3, genital warts, some anal cancer, vaginal vulvar cancer, and oropharyngeal cancer. Cervical cancer treatment costs averted were calculated using the number of cervical cancer cases prevented by vaccination and the estimated cost per case of cervical cancer. The number of QALYs saved by vaccination was calculated using the age-specific number of cervical cancer cases averted by the vaccine and the estimated number of QALYs lost per case of cervical cancer. The study found that cost per QALY gained by adding routine vaccination of 12-year-old girls to current cervical cancer screening ranged from $3906 to $14723.[25] Given the cost per QALY gained is less than $50,000,

HPV vaccination is cost-effective in the United States. A similar study out of Canada examining HPV vaccination in 12-year-old females also found HPV vaccination to be cost-effective. The Canadian study estimates $18672 to $31687 per QALY gained and approximately 390 to 633 prevented cervical cancer cases.[26]

The cost-effectiveness of HPV vaccination has also been well studied globally. In a 2014 study, 179 countries were examined using the Papilloma Rapid Interface for Modeling and Economics (PRIME) model. The PRIME model estimates the health and economic effect of vaccination in terms of age-dependent incidence of cervical cancer and mortality in direct proportion to vaccine efficacy against HPV 16 and 18. Results of the study were validated by comparison with 17 other published studies and all 72 published GAVI-eligible countries. The study found that HPV vaccination was very cost-effective in 156 (87%) out of 179 countries.[27] Another study published in 2021 was a meta-regression analysis looking at cost-effectiveness of HPV vaccination in 195 countries. The study analyzed previously published cost-effectiveness analyses. Factors were analyzed at the country, intervention, and method level and to predict incremental cost-effectiveness ratios (ICERs). The mean predicted ICER was 4217 United States Dollars (USD) per disability-adjusted life-years (DALY, an estimate of overall disease burden considering healthy years of life lost secondary to a given disease), averted globally. ICER was lowest in sub-Saharan Africa and South Asia with a mean of $706 USD per DALY averted and $489 per DALY averted across 5 countries.[28] These numbers confirm that use of the HPV vaccine in sub-Saharan Africa and in South Asia is extremely cost-effective and a prudent investment well worthy of competing for scarce public health dollars.

Equity

As with most of the health care today, HPV and cervical cancer are not exempt from issues of health equity, access, and commercialism. In May of 2018, the WHO issued a call to action to eliminate cervical cancer as a public health problem. The WHO has created the cervical cancer elimination initiative and adopted the global strategy for cervical cancer elimination in August of 2020. Vaccination is one of the WHO's 3 key pillars in achieving cervical cancer eradication. As previously mentioned, the vaccination target set by the WHO call for 90% of girls to be fully vaccinated by the age of 15 years by the year 2030.[29] As of 2020 less than 25% of low-income countries had implemented HPV vaccination compared with 85% of high-income countries.[30]

There are several factors that have made expanding access to vaccination challenging, among which is the global HPV vaccine shortage. In the 2020 UNICEF Human Papillomavirus Vaccine: Supply and Demand Update, UNICEF breaks down some of the factors influencing global shortage. At the time of their analysis, there were only 2 manufacturers the WHO has qualified for HPV vaccines, Merck and GlaskoSmithKline. The analysis estimated that in 2020 the global market would require 44.5 million doses of HPV vaccine, up significantly from the 30 to 35 million doses per year from 2010 to 2016.[15] Factors that have contributed to the increase in demand include the introduction of vaccine to India and China, increase in gender neutral immunization policies, and the WHO call to end cervical cancer that has stressed the need for equitable access to HPV vaccine.[31] With only 2 manufacturers, supply has struggled to keep up with demand, and it is predicted this shortage will continue for the near future.

The COVID 19 pandemic has also had a substantial negative impact on efforts at expanding HPV vaccination. Much of the infrastructure used for vaccination globally uses locations where communities gather such as schools, community centers, and places of worship. Closures and limitations on gathering have resulted in millions of girls missing out on vaccination. The pandemic also caused a massive reallocation

of public health resources away from routine immunization and toward the global pandemic. According to a study by UNICEF and WHO, the COVID-19 pandemic resulted in 23 million children missing out on scheduled vaccination and 1.6 million girls missing out on HPV vaccinations in 2020.[32] In a recent study, the long-term effects of missed HPV vaccines in the United States during the COVID pandemic is estimated evaluating vaccine uptake data from January 2018 to August 2020 and applies it to 4 different scenarios for post-COVID vaccination catch up. With the most optimistic vaccine recovery there are 130,000 additional cases of genital warts, 22,000 cases of CIN1, and 48,000 cases of CIN2/3 over the next 100 years. More than 50% of the cases of genital warts, CIN 1, and CIN2/3 would occur in the next 25 years. The scenarios also project an associated increase in cervical cancer cases. In the most optimistic projection of these increases, there are 2882 additional cases of cervical cancer, with 66% occurring in the first 50 years.[33]

LITTLE KNOWN FACTS ABOUT HUMAN PAPILLOMAVIRUS AND HUMAN PAPILLOMAVIRUS VACCINATION

As we continue to learn more about HPV, there have been some unexpected discoveries. For instance, an association between coinfection with HPV and Trichomonas vaginalis and an increase in the risk of CIN have been demonstrated. More specifically, the study found that although coinfection with Candida or Gardnerella with HPV did not have as association with CIN, *T vaginalis* coinfection was associated with both more oncogenic HPV strains and an increase in the risk of CIN 1 by an odds ratio (OR) of 1.8 and CIN 2/3 by an OR of 1.71.[34]

Male circumcision has also been researched in association with HPV. Circumcision has been well studied in sub-Saharan Africa with HIV acquisition and transmission, and this research is actively expanding to other STIs. Most of the data show a protective association between male circumcision and risk of HPV infection in both African and European settings.[35] Male circumcision has also been shown to reduce the risk of oncogenic HPV genotypes and cervical cancer.[36]

The Long View

Australia could serve as one of the first examples of what cervical cancer eradication could look like. As previously discussed, Australia was one of the first countries to introduce a national HPV vaccination program in 2007 and did so for a wide age range from 12 to 26 years with a school-based program.[20] Australia has also had a national cervical cancer screening program since 1991, which has resulted in an approximately 50% decrease in cervical cancer incidence.[37] In a modeling study in 2019, it was estimated that by 2028 the incidence of cervical cancer in Australia will be fewer than 4 new cases per 100,000 women and less than 1 per 100,000 by 2066. Further, by 2034 the cervical cancer mortality is projected to decrease to less than 1 death per 100,000 women.[38] Australia is thus a clear example of the immense potential impact of prioritization of HPV vaccine uptake with the goal of eradication of cervical cancers by a multitude of public health entities. Eradication, or near eradication, is possible.

SUMMARY

The HPV vaccine is an unprecedented tool to prevent HPV-mediated cancers, of which, cervical cancer has the largest global burden of disease. The cost of the HPV vaccine, inequitable access, delivery challenges, and a global supply shortage, combined with the stigma of talking about and preventing a “below the belt” cancer, have kept it from becoming the cancer prevention miracle that it is. However, with the

WHO's call to eliminate cervical cancer elevating the global discussion about this vaccine, as well as efforts to increase HPV vaccine supply, in so facilitating lower pricing and improving access, and creative determination to increase its use, we can look forward to more individuals able to access this Cancer Moonshot.

CLINICS CARE POINTS

- HPV is a common virus that is sexually transmitted and has 14 subtypes that cause cancer.
- Of the HPV virus types, HPV 16 and HPV 18 combined account for 70% of cervical cancer.
- All HPV vaccines offer protection against HPV 16 and HPV 18 when the vaccine is given before exposure to these viruses.
- One HPV vaccine, the nonavalent HPV vaccine, in addition to protecting against HPV types 16 and 18, also offers protection against HPV types 31, 33, 45, 52, and 58. This vaccine protects against 90% of cervical cancer.
- Because the HPV vaccine works to prevent infection (versus eliminate infection once it is present), the best time to give the HPV vaccine is in the 9 to 14 years age range.
- When given to individuals younger than 15 years, 2 doses are approved, given 6 to 12 months apart, although the WHO also has stated that 1 dose of HPV vaccine may be considered in individuals 20 years of age or younger (instead of 2 doses).
- For individuals 15 years old or older, or for individuals who are immunocompromised, 3 doses of the HPV vaccine are needed, with the second dose 1 to 2 months after the first dose and the third dose 4 months after the second.

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