Title: Global Delivery of Human Papillomavirus Vaccines

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Abstract/Summary: Worldwide, cervical cancer is the fourth most common cancer among women, with over half a million women diagnosed with cervical cancer in 2012. Human papillomavirus (HPV) vaccination, if broadly implemented, has the potential to significantly reduce global rates of morbidity and mortality associated with cervical and other HPV-related cancers. Over 100 countries around the world have licensed HPV vaccines. As of February, 2015, there were an estimated 80 national HPV immunization programs and 37 pilot programs, including many implemented in low- and middle-income countries. In this article, global implementation of HPV vaccination programs is discussed, including successes and ongoing challenges. Issues such as vaccine financing and different approaches to HPV vaccine delivery are presented.

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Key Points:

- As of 2012, over 100 countries had licensed HPV vaccines and as of February, 2015 there were an estimated 80 national HPV vaccination programs and 37 pilot programs
- Financing mechanisms through Gavi, the Vaccine Alliance, and the Pan American Health Organization have helped a number of low- and middle-income countries (LMICs) implement HPV vaccination programs, though funding challenges continue to represent a significant barrier in many countries.
- School-based approaches to HPV vaccine delivery have generally been very successful in both LMICs and high-income countries.
- Clinic- or office-based delivery strategies have been evaluated, with some countries showing limited success (e.g., the U.S.) and others having greater success (e.g., Denmark).
- Community outreach approaches have shown some success in HPV vaccine uptake, particularly in reaching children not in school

Introduction

Worldwide, genital human papillomaviruses (HPV) are very common. In most cases HPV infections are symptomless and do not progress to disease, however, persistent HPV infection can progress to cause genital warts (via non-oncogenic or low-risk types), as well as cancers of the anogenital area and head and neck (via oncogenic or high-risk types).[1] Worldwide, HPV types 16 and 18 are causally implicated in the development of approximately 70% of cervical cancers, whereas HPV types 6 and 11 cause about 90% of genital warts.[1] Globally, cervical cancer is the fourth most common cancer among women. In 2012, an estimated 527,624 women were diagnosed with cervical cancer and more than 85% of the 265,653 deaths occurred in developing countries (see Fig. 1).[2,3] In the U.S. it is estimated that over 17,000 women and over 9,000 men are diagnosed with HPV-related cancers each year (see Table 1).[4]

Table 1: U.S. burden of HPV-related cancers in men and women

Type of Cancer	Average annual number of cases	Cases probably caused by HPV
Cervix	11,422	10,400
Vagina	735	600
Vulva	3,168	2,200
Anus (W)	2,821	2,600
Oropharynx (W)	2,443	1,800
Total Females	20,589	17,600
Penis	1,048	700
Anus (M)	1,549	1,400
Oropharynx (M)	9,974	7,200
Total Males	12,571	9,300

Source: Centers for Disease Control and Prevention, United States Cancer Statistics (USCS), 2006-2010. Available at: http://www.cdc.gov/cancer/hpv/statistics/cases.htm

There are currently three vaccines that prevent HPV infections and diseases: a bivalent vaccine (HPV2) that protects against types 16 and 18,[5] a quadrivalent vaccine (HPV4) that protects against types 16, 18, as well as 6 and 11,[6,7] and a 9-valent vaccine (HPV9) that protects against the four types covered in HPV4, plus five additional oncogenic types (31, 33, 45, 52, and 58).[7] HPV vaccine efficacy, effectiveness, and safety are well-established.[9-12]

Insert Fig. 1 Here

Key points on HPV vaccines:

- As of 2012, over 100 countries had licensed HPV vaccines[13]
- As of February, 2015 there were an estimated 80 national HPV vaccination programs and 37 pilot programs, with many of these implemented in low- and middle-income countries (LMICs; see Fig. 2)[14]
- The 9-valent HPV vaccine was licensed by the United States Food and Drug Administration in December, 2014[15]
- The World Health Organization (WHO) recommends a 2-dose vaccination schedule for those under 15 years of age[16]
- The U.S. continues, for now, to recommend a 3-dose schedule, regardless of age[8]

In the United States (U.S.), the national goal for HPV vaccination 3-dose series completion is 80% of males and females.[17] However, the 2013 National Immunization Survey-Teen found that only 37.6% of females and 13.9% of males ages 13-17 years had received ≥3 doses of the vaccine.[18] In contrast, other high income countries (HICs) like Canada, the United Kingdom (U.K.), Denmark, and Australia have achieved very high HPV vaccination rates, as have several LMICs (see Fig. 2).[19-25] The relative success or failure of HPV vaccination programs is likely due to many factors, including vaccine funding, implementation approaches, logistical and resource barriers, and cultural and political issues related to vaccination. We will address these factors in the sections below.

Insert Fig. 2 Here

HPV Vaccine Funding

HPV vaccine cost is a central factor in successful implementation of vaccination programs. High out-of-pocket costs for individuals decrease HPV vaccine acceptability[26-28] and high costs for LMICs may limit their ability to provide vaccine for their citizens. The cost for the vaccine in the public sector ranges by country and region, from U.S. $4.50 to over U.S. $100 per dose,[29] representing a potential barrier to its implementation in many countries worldwide.

Significant progress has been made to improve the affordability of HPV vaccine to LMICs through financing mechanisms including Gavi, the Vaccine Alliance, and the Pan American Health Organization (PAHO) Revolving Fund. Merck and Co., announced in June 2011 that HPV4 would be offered to Gavi for U.S. $5 per dose for GAVI-eligible countries,[30] and in 2013 a further record low price of U.S. $4.50 per dose was announced.[31] Many Gavi-eligible countries are able to procure the vaccine for a small co-payment of U.S. $0.20 per dose,[32] increasing affordability. However, this low cost is only available to the 49 LMICs that are currently eligible for Gavi support, which have a gross national income per capita in 2015 below U.S. $1,580.[33] Countries that have successful experiences delivering HPV vaccines to adolescents are eligible to apply to Gavi for financial support for national implementation or if additional experience is required can apply for support to implement demonstration projects.[29,34] The cost to procure the HPV vaccine for LMICs in Latin America and the Caribbean through the PAHO Revolving Fund is approximately U.S. $10-15.[32,35] The PAHO Revolving Fund was established in 1978 as a mechanism for procurement of supplies and equipment necessary for sustained delivery of vaccines.[36]

The cost for the vaccine and delivery approach of HPV vaccine programs has been found to vary by country and delivery approach.[32,35,37,38] Reasons for variation in cost between pilot projects included: scope and scale, delivery strategy, national income levels and public health cost, infrastructure and the compensation structure for health staff, and health system policies. A recent study comparing the costs of HPV pilot, demonstration or national programs in Peru, Uganda, Viet Nam, India, Bhutan and Tanzania found that introduction costs per fully immunized girl ranged from $1.49 to $18.94, with recurring costs from $1.00 to $15.69.[37] Despite subsidization of the HPV vaccine for many LMICs, costs to deliver and

sustain HPV vaccination programs remain a significant on-going investment and potential financial barrier. In addition, although significant progress has been made to achieve lower prices for the vaccine, many middle-income countries are ineligible for low prices and co-payment systems offered through Gavi, or may have 'graduated' from Gavi-eligibility. These countries may continue to experience barriers to fund and sustain HPV vaccination programs and opportunities to support these countries should be investigated.[39]

In HICs vaccine financing varies greatly, from a patchwork combination of private and public funding in the U.S. to publically-funded programs in, for example, Canada, Australia, the U.K., and several other European countries.[13] Not all European countries provide public financing for HPV vaccine, however, and several require self-pay.[40]

HPV vaccination implementation approaches

School Based Approaches

School-based delivery methods have been an effective approach to achieve high coverage in several LMICs through demonstration projects, donation programs and national vaccination programs.[23,25,38,41-43] Demonstration programs through the international non-governmental organization PATH have achieved high coverage through school-based delivery in Peru (82.6%), Uganda (88.9%) and Vietnam (96.1%).[42] High coverage has also been seen in school-based demonstration projects in South Africa,[44] Brazil,[45] and Nepal.[24] The Gardasil Access Program (GAP) was implemented by Axios Healthcare Development, and received small donations of vaccine by Merck & Co., to support countries to gain experience in the design and implementation of HPV vaccination programs.[38,46] Between 2009 and 2012, 21 vaccination programs were implemented in 14 LMICs around the world.[38] The GAPs achieved an average vaccine uptake rate of 88.7% through three delivery strategies including school-based, facility-based and mixed approaches. The school-based strategy was specifically identified as a factor that positively influenced their vaccine uptake rates.[38] Lastly, in 2011, national implementation of the HPV vaccine in Rwanda achieved 93.2% coverage for girls in grade six, through school-based vaccination and community sensitization and involvement.[23]

School-based HPV vaccination programs have also been implemented successfully in several HIC, including the U.K., Australia, and Canada.[19-21] Of the European countries that report an organized HPV vaccination program, over 50% utilize a school-based delivery approach.[40] In the U.S. there has been very limited implementation of school-based HPV vaccination, though this approach has been identified as an ideal way to reach the largest number of adolescents.[47] A pilot school-based adolescent vaccination initiative evaluated in Chicago, IL, was only modestly successful in delivering HPV vaccination, with obstacles including difficulty getting informed consent forms returned from parents and inconsistent participation by schools over time.[48] In some areas of the U.S., vaccines, including HPV vaccine, can be delivered via school-based health centers (SBHCs). However, while this approach eliminates some barriers to vaccination, vaccines are delivered on an individual patient basis and therefore SBHC-delivery is not as efficient as an approach that involves administration of vaccines on a single day to groups of youth.[49] Attitudes of key stakeholders in the U.S. (e.g., parents, school nurses, school administrators) about the feasibility of school-based HPV vaccination implementation are mixed, with some research showing relatively little concern among parents and administrators[48] and other research indicating uncertain support and doubts about program implementation.[50]

Clinic/Office-based Approaches

The principal approach to HPV vaccine delivery in the U.S. and a number of European countries is via medical clinics and doctors' offices. Office-based vaccination is standard practice for most childhood vaccines in the U.S. For vaccines required for school-entry, this approach has generally been quite successful, with high levels of vaccination coverage achieved.[51] However, with the exception of the state of Virginia and the District of Columbia , HPV vaccination is not required for school entry.[52] Moreover, Virginia has a relatively weak HPV vaccine school entry law, which has not proven to be particularly effective.[18,53] Without a clear public health policy supporting HPV vaccination, the burden of decision-making and recommendations largely falls on health care providers (HCP) and parents. As a result, despite the licensure of HPV4 in 2006 and public and private financing for vaccination, HPV vaccination rates in the U.S. remain at lower than desired levels.[18]

Reasons for non-vaccination appear to be related to unwarranted parental concerns about safety, failure of HCPs to make strong, routine recommendations for vaccination at the targeted ages of 11-12 years, lack of knowledge, and access issues (particularly for follow-up doses).[54-57] See Box 1 for a list of factors that have been identified as barriers to HCPs making a strong recommendation for HPV vaccination.

Box 1: Health Care Provider Barriers to Recommendation of HPV Vaccine for Adolescents

- Limited knowledge and understanding of HPV-related disease, particularly in males
- Concerns of the vaccine's safety and efficacy
- Uncomfortable discussing sexual behavior with young adolescents
- Preference for vaccinating older adolescents (potentially linked to discomfort on discussing sexual behavior)
- Apprehension of parental resistance
- Insufficient time available to discuss vaccines
- Inadequate systems to remind health care providers to recommend vaccines to age-appropriate patients

Source: National Foundation for Infectious Diseases. Call to Action: HPV Vaccination as a Public Health Priority. August 2014. Available at: http://www.adolescentvaccination.org/hpv-cta

A variety of intervention approaches have been explored, including the use of electronic health message prompts directed to HCPs,[58,59] reminder messages sent to parents and adolescents,[60-63] communication messaging targeting parents and youth,[64] and practice-based interventions.[65-68] Results of these interventions have been mixed, with some showing modest improvements in vaccination rates and others showing no significant effects.[64,69]

In contrast to the U.S. experience, Denmark, which also uses an office-based approach to HPV vaccination, has had remarkable success. In 2009, Denmark began providing free HPV vaccine for all 12 year old girls. After just one year, 80% of eligible girls had initiated vaccination and 62% had received all three doses of vaccine.[22] Over time, even greater success was achieved in Denmark, with over 90% of girls receiving ≥ 1 dose of vaccine and over 80% completing the 3-dose series.[70] Interestingly, even with this impressive level of success, HPV vaccination rates in Denmark are significantly lower among girls from immigrant families and among those from families with fewer socioeconomic resources.[70]

Community Outreach Approaches

Community outreach delivery strategies, which have principally been implemented in LMICs, have demonstrated some success reaching out-of-school girls or providing opportunities for vaccine catch-up services, particularly in countries with low school enrolment and poor attendance.[25,42,43] Community approaches are also generally paired with other strategies for a mixed approach to achieve vaccination. A school-based vaccination program in combination with existing community-based child-focused public health campaign was used in Uganda, in order to reach out-of-school girls.[42] Coverage through this approach only achieved 52.6% for their population during the first year.[42] In Vietnam, both community health center and school-based strategies were tested over two years and both approaches achieved high HPV vaccination coverage.[71] Achievement of high coverage in Rwanda's national HPV vaccine program has also been attributed to the combination of a school-based vaccination program, high levels of community involvement to identify absent or out-of-school girls, as well as strong national sensitization efforts and outreach prior to the initiation of the campaign.[23]

The PATH demonstration project in India achieved high coverage through a mixed approach using school and health center-based delivery using existing immunization programs (68% urban, 83% rural coverage), as well as special public health campaigns at three fixed time points (77-88% coverage).[41,42] Despite these achievements in India, adverse events were falsely linked to the vaccine and the demonstration project was incorrectly characterized as an experimental clinical trial.[72,73] These claims were refuted, citing that appropriate review and approvals were obtained, that extensive research on the safety found no deaths related to the HPV vaccine, and that demonstration projects are not clinical trials.[74,75] Nonetheless, the PATH program was suspended by the Ministry of Health and Family Welfare,[72,76] a decision highlighting potential inadequate recognition of public distrust and a history in India of justifiable suspicion of the motives of outside organizations.[77,78] Findings from demonstration and national programs highlight the importance of incorporating community outreach and sensitization to the successful implementation of the HPV vaccine in LMICs.

Challenges and Future Directions

Understanding and addressing the potential logistical and sociocultural challenges has been, and continues to be critical to ensuring the acceptability and effectiveness of HPV vaccine programs worldwide.

Logistical and resource barriers with vaccine delivery:

- Health system capacity and infrastructure, including cold chain systems to transport and store the vaccine, as well as the availability of human resources for cold chain and logistics management;[41,79]
- Financial costs to introduce and sustain HPV programs;[37]
- Girls (including pre-adolescents and adolescents) represent a new population that has not been regularly targeted for routine immunization by the Expanded Program on Immunization;[25]
- School-based programs may experience challenges including: absenteeism, determining eligibility for vaccination (e.g. grade versus age-based criteria), capturing out-of-school girls, coordination of diverse immunization and education stakeholders, as well as scheduling three doses during the academic year; [25,42,80]
- Delays or lags in delivery of vaccination programs, caused by stock outs may decrease interest among girls and parents to complete all doses;[38]
- Straining health systems and human resources by introducing new vaccines, including the HPV vaccine.[71,81]

Cultural and political barriers

Sociocultural challenges to implementation and delivery of the HPV vaccine highlight the importance of improving attitudes and knowledge of HPV, HPV related diseases, and awareness of the vaccine and vaccination programs. For example, as discussed previously the PATH demonstration project in India demonstrates problems that may occur related to not fully understanding the cultural constructs when implementing vaccine programs.

Other potential cultural and political challenges to HPV vaccine delivery may include:

- Stigma and controversy, targeting female adolescents ages 9-13 years for a sexually transmitted infection;[79,82]
- Parental concerns over the vaccines' safety and its potential side effects, including unjustified fears of future infertility, early sexual debut, and potential for increased sexual activity;[83-85]
- Differences in acceptable communication strategies and dissemination of health information, as well as parental consent preferences (e.g. opt-in versus opt-out);[86]
- Skepticism and concerns related to research and introducing new vaccines and medicines;[86]
- Political will and commitment of decision makers to prioritize demonstration projects and/or national implementation of the HPV vaccine[87]

In order to influence the acceptability and uptake of the vaccine in all countries it is critical to provide information and improve knowledge of the intervention. In Africa, despite low levels of knowledge or awareness of HPV (on average 26%), and the HPV vaccine (15%), high levels of acceptability were achieved across 10 countries (59-100%) due to the vaccine's accessibility, costs and cues to action by health workers and decision makers.[85] Another systematic review supported findings that high levels of willingness to vaccinate and acceptability of the HPV vaccine can be achieved, despite low levels of knowledge and awareness of HPV, the vaccine or cervical cancer.[88] Early experiences from demonstration projects in Peru, Viet Nam, Uganda and India also found limited initial awareness and inadequate information of cervical cancer, HPV, the HPV vaccine and the vaccination program prior to community sensitization efforts.[42] Adequate community engagement and sensitization are key factors in successful implementation and overcoming sociocultural barriers.[23,38,42,83,89]

Future directions

With progress in HPV science and continued work towards global herd immunity, challenges will continue to transform and change as countries both achieve greater vaccination rates and encounter new barriers towards adopting a comprehensive approach. In 2014, the U.S. CDC and the President's Cancer Panel identified adolescent HPV vaccine uptake as a public health priority to prevent HPV-related cancers and recommended key strategies to HCPs (see Box 2).[57] The National Foundation for Infectious

Diseases in collaboration with multiple stakeholders have developed a comprehensive online educational resources related to HPV and HPV vaccines for HCP (adolescentvaccination.org/hpv-resource-center)

Box 2: Recommendations and key strategies for health care providers to improve HPV vaccination rates

- Recommend the HPV vaccine with the same strength and conviction used to recommend other adolescent vaccines. A recommendation by a health care provider is the most important reason that adolescents get the HPV vaccine.
- Health care providers should recommend the vaccine with a presumptive, rather than participatory style to improve parental acceptance of the vaccine
- Emphasize that the HPV vaccine prevents cancer
- Health care providers should educate themselves on HPV and HPV vaccines
- Address potential barriers through key elements of HPV education including: 1) provide sufficient information to parents on the disease and cancer prevention, 2) outline the rationale for vaccinating ages 11-12, 3) discuss safety and efficacy of the vaccine, 4) remind parents/patients of the 3-shot series, 5) address system barriers (e.g. cost), and 6) highlight the benefit of male vaccination.
- Inform colleagues and staff to ensure that everyone delivers the same messages on HPV
- Communicate vaccination benefits to parents and adolescents at every opportunity
- Make vaccination procedures routine and focus on ways to reduce missed opportunities

Source: National Foundation for Infectious Diseases. Call to Action: HPV Vaccination as a Public Health Priority. August 2014. Available at: http://www.adolescentvaccination.org/hpv-cta

Future challenges to, and directions for, HPV vaccine implementation in LMIC may include:

- Meeting the WHO 2014 guidelines on cervical cancer, and introducing the HPV vaccine within a comprehensive cervical cancer prevention and control strategy and program;[90]
- Delivering the HPV vaccine in conjunction with other non-vaccine interventions targeting adolescents, for example iron supplementation;[91]
- Potential risks for health disparities with unequal distribution of HPV vaccination globally, particularly with the introduction of the 9-valent vaccine;
- Potential changes to cervical cancer screening programs and protocols in the post vaccination era;
- Changes to vaccine administration programs related to 2-dose HPV vaccination, which is now recommended by the WHO for youth ages 9 to 13 years;[17]

- Potential risk for lower public acceptance due to changes in vaccine composition and dosing schedules.

Conclusion

Pilot, demonstration and national HPV vaccination programs have successfully achieved high coverage and vaccine uptake among many countries worldwide. Financing mechanisms have improved the affordability of the vaccine in these settings and drastically contributed to overcoming this barrier to implementation in many countries. LMICs have achieved success through the introduction of diverse delivery strategies, including school-based approaches and community engagement and sensitization. Among many HICs success has also been achieved with diverse delivery strategies, including school-based and clinic/office-based approaches, as evidence by the success in Australia, Denmark, and the U.K. among others. The U.S. continues to have a slow but steady rise in vaccination rates with primarily a clinic/office based approach. Nearly a decade after the first HPV vaccine was made available, considerable progress to global delivery has been achieved, however, continued efforts to address challenges and share successes will be critical to ensure equitable and universal access to the HPV vaccine globally.

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Fig. 1. Age-standardaized incidence rates per 100,000 of cervical cancer in the world (estimations for 2012). From: Ferlay J., Soerjomataram I., Ervik M., Dikshit R., Eser S., Mathers C., Rebelo M., Parkin D.M., Forman D., Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on May 19, 2015.

Fig. 2. Global progress in HPV vaccine introduction (February, 2015). From: Cervical Cancer Action. Global Maps: Global Progress in HPV Vaccination. 2015. Available at: http://www.cervicalcanceraction.org/comments/comments3.php. Accessed May 27, 2015.

Table 1. U.S. Burden of HPV-related cancers in men and women

Source: Centers for Disease Control and Prevention, United States Cancer Statistics (USCS), 2006-2010. Available at: http://www.cdc.gov/cancer/hpv/statistics/cases.htm

Box 1. Health care provider barriers to recommendation of HPV vaccine for adolescents

Source: National Foundation for Infectious Diseases. Call to Action: HPV Vaccination as a Public Health Priority. August 2014. Available at: http://www.adolescentvaccination.org/hpv-cta

Box 2. Recommendations and key strategies for health care providers to improve HPV vaccination rates

Source: National Foundation for Infectious Diseases. Call to Action: HPV Vaccination as a Public Health Priority. August 2014. Available at: http://www.adolescentvaccination.org/hpv-cta