Is Universal Implementation of Human Papillomavirus Vaccination Feasible? An Analysis of the Barriers to Primary Prevention Strategies for Cervical Cancer

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Human Papillomavirus (HPV) vaccination should be included in national immunization programs, as part of a comprehensive approach to cervical cancer prevention and control. The practical aspects of vaccine uptake are now the most important issue in HPV vaccine research from a public-health perspective. Increasing uptake, specifically in regions where disease burden is highest, will require thoughtful consideration of cost-effectiveness, innovative financing mechanisms, novel approaches to vaccine vehicle delivery and public acceptance. We review ongoing critical barriers and challenges to implementation of HPV vaccination. The aim of this paper is to review ongoing critical barriers and challenges to implementation of HPV vaccination.

Keywords

Human Papillomavirus vaccination, HPV, barriers to HPV vaccination

Abstract

1. Introduction

1.1 Aims

Cervical cancer is the leading cause of cancer in many resource-limited countries. Human papillomavirus (HPV) infections are linked with the development of cervical cancer. A vaccine that immunizes women against the possibility of malignant transformation would change the demographics of cancer development worldwide. Despite the development of an HPV vaccine, national vaccination programs are limited. This review analyzes the barriers to universal vaccination against HPV.

1.2 Summary of the role of Human Papillomavirus infection in the development of cervical cancer Human papillomavirus (HPV) infection with high-risk subtypes has been established as the primary etiologic agent in cervical neoplastic transformation (Walboomers et al., 1999). Virtually 100% of cervical cancers, squamous, adenosquamous, and adenocarcinomas, are now thought to be associated with HPV infections. The term "high-risk (HR)" is used to label oncogenic genital-specific HPV subtypes that have been associated with malignant transformation in the lower genital tract. Pooling information from eleven case-control studies over nine countries, fifteen HR-HPV types were identified in the cervical cancers and included HPV -16,-18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -68, -73, -82 (Muñoz et al., 2003). Further, HR- HPV subtypes 16 and 18 are implicated in 65-70% of new cervical cancers worldwide (Agostie et al, 2007).

Clinical trials have demonstrated that vaccines targeted against HR HPV subtypes can be 95% effective in preventing HPV-16 or -18 persistent infection and at least 93% effective in preventing vaccine type-specific cervical lesions (Future II, 2007; Garland et al., 2007). Two prophylactic vaccines, the quadrivalent which target HPV types 6,11,16,18 (Gardasil, Merck) and the bivalent which targets HPV types16, 18 (Cervarix, GSK), demonstrate high immunogenicity, tolerability and efficacy against HPV-16 or -18 infections (GlaxoSmithKline Vaccine HPV-007 Study Group, 2009). The 2013 National Health and Nutrition Examination Survey reported a greater than 50% decrease in HPV infections caused by HPV 6, 11, 16, and 18 in girls aged 14–19 years within the first 4 years of HPV vaccination program (Markowitz et al., 2013).

These and other data demonstrate high potential for HPV vaccination to alleviate the burden of HPV-related disease. Indeed, he use of prophylactic HPV vaccine in pre-adolescent girls and young women for primary prevention of cervical cancer, and potentially other HPV-related cancers (anus, vulva, vagina, head- and neck), was endorsed by the US Food and Drug Administration and European Medicines Agency (EMEA) in 2006 (quadrivalent vaccine) and 2007 (bivalent vaccine). In April 2009, the World Health Organization [WHO] issued a position paper on Human Papillomavirus vaccination, recommending that the vaccination be included in national immunization programs, as part of a comprehensive approach to cervical cancer prevention and control (Dorleans et al., 2010; World Health Organization [WHO], 2009). A nonavalent HPV (9vHPV) vaccine which effectively covers HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 has been recommended by the Advisory Committee on Immunization practices for routine vaccination (Joura et al., 2015; Petrosky et al., 2015). HPV vaccination can play a critical role in cancer prevention, especially

in low-income countries where disease burden is highest, and access to secondary and tertiary prevention is limited. While developing countries are eager to implement HPV vaccination within existing vaccination programs, this cannot occur unless vaccine introduction is programmatically feasible, economically sustainable and where cost-effectiveness aspects have been duly considered (Ferlay et al., 2012). No medical intervention has such an unambiguous track record of preventing morbidity and mortality from infectious disease as that of vaccines (Kim, Sweet, Chang, & Goldie, 2011). A review of 20 studies on the population-level consequences and herd effects after HPV vaccination demonstrated that in countries where HPV vaccination coverage was at least 50%, HPV 16 and HPV 18 infections decreased significantly after the institution of vaccination programs (Drolet et al., 2015).

Vaccination coverage for HPV vaccine varies by country (Owsianka & Gańczak,2015). Widespread implementation of HPV vaccination has the potential to save 12.6 per 1,000 lives. however, substantial barriers limit incorporation of HPV vaccination into national health agendas. In the United States, for example, only 33 to 41 % of adolescents receive HPV vaccines (Hill et al., 2015). In this article, we review ongoing critical barriers and challenges to implementation of HPV vaccination, specifically in resource-constrained settings.

2. Implementation Barriers And Challenges To

Challenges to HPV vaccination will differ according to societal and resource constraints of each country. In the high-income countries with a significant portion of the gross national product devoted to health care, barriers to vaccination are commonly associated with parental and community fears and lack of trust (Organization for the Economic Cooperation and Development (OECD), 2014). In low and middle-income countries (LMICs), these cultural attitudes are compounded by the lack of medical infrastructure, healthcare financing, and delivery systems for vaccines make up a sizable portion of the barriers to HPV vaccination.

2.1 Social Ecology and Barriers to Access to Cervical Cancer Screening

The socio-ecological model of barriers to health care can be used to analyze the barriers to cervical cancer screening (Goodman, 2013). The levels of barriers range from intrapersonal, interpersonal, organizational, community, and society. At the intrapersonal level, personality, comprehension, and genetics are factors to decision-making and access to health care. At an organizational level, employment, the level of education and access to health insurance are important. The factors of race and ethnicity, socioeconomic status and public resources including healthcare facilities play a role at a community level. The policy is the leading factor associated with healthcare barriers at a society level. The socio-ecological model can also be used to analyze the barriers to HPV vaccine uptake (Ferrer, Trotter, Hickman, & Audrey, 2014). Also, at each socio-ecologic level, cross-cutting themes of the mandate, finance, sexual mores, trust, and consent play a role in HPV vaccine uptake. The economics, policy, and delivery systems of HPV vaccination are fertile grounds for the success of universal vaccination programs.

2.2 Cost-Effectiveness, Financing, and Sustainability

2.2.1. Affordability

Affordability and cost-effectiveness are the largest barriers to access; at a price of $130-$255 per vaccine or at minimum, $390 per woman immunized, countries have not had the resources to allocate limited health budgets to a vaccine with unproven cost effectiveness.

In May 2013, the GAVI Alliance, (formerly the "Global Alliance for Vaccines and Immunisation"), announced plans to launch demonstration projects to implement HPV Vaccination in eight sub-Saharan countries by which these countries will have access to the vaccination at record low costs: $4.50 Merck's Gardasil and $4.60 GSK Cervarix. While the cost decrease is dramatic, it is not attainable for most low-income countries (Global Alliance for Vaccines and Immunisation (GAVI), 2013). It is estimated that the per-cost dose should be $1-$2 (including wastage, administration, program support) to make vaccination both cost effective and affordable (Goldie, O'Shea, Diaz, & Kim, 2008). One suggestion is on increasing efforts directed towards secondary prevention. Models suggest that at current costs, vaccination is less cost effective than the provision of secondary prevention once or twice per lifetime to women at risk (Louie, de Sanjose, & Mayaud, 2009; Agosti & Goldie, 2007; Goldie, O'Shea, Diaz, & Kim, 2008). In Thailand, a recent mathematical model determined the efficiency of HPV and cervical cancer incidence rates and pre-adolescent HPV vaccination with one to five-lifetime screening interventions if vaccination costs could be lowered (Sharma, Ortendahl, van der Ham, Sy, & Kim, 2012). A study that evaluated resources in the Philippines found that high screening coverage with visual inspection with acetic acid was the most cost effective strategy. The addition of vaccination is potentially cost effective if administered to 11-year-olds but current costs of vaccination limit this option (Guerrero et al., 2015).

2.2.2. Existing Financing Mechanisms

Existing HPV vaccination financing and introduction mechanisms are diverse. While most low- and middle-income countries have licensed the vaccines, the financing of HPV vaccination has varied (Batson, Meheus, & Brooke, 2006). It has been done through the public sector in Mexico, Panama, Romania, Marshall Islands, and Palau, through district level demonstration and research projects in Uganda, Vietnam, India, and Peru, and by industry donation in Bhutan, Fiji, Lesotho, Nepal, Rwanda, and Tanzania. For recipients of industry donations, sustainable financing remains a significant barrier for continued access in these countries. For countries without existing plans for financing, country-based epidemiologic data will be needed to determine the burden of cervical cancer in order to inform vaccination policy and costing (Batson, et al., 2006).

2.2.3. Sustainable Financing Vaccination Strategies

HPV vaccine financing can harness the lessons learned from past initiatives by utilizing novel financing techniques to reduce cost and improve access. One such example is the utilization of Advanced Market Commitments, which was successfully piloted for the pneumococcal vaccine. An Advanced Market Commitment (AMC) incentivizes manufacturers to invest in scaling-up production capacity to meet demands of developing countries. An AMC can also accelerate vaccine coverage by ensuring predictable vaccine pricing by the binding commitment of participating companies to supply the vaccine at low, long term, sustainable prices and overall, to

contribute to a sustainable supply market (Global Alliance for Vaccines and Immunisation (GAVI), 2011). In the case of the pneumococcal vaccine, the AMC brought together three key factors: industry commitment, country readiness and GAVI financing to overcome cost barriers (GAVI, 2013). A total of 100 million doses of pneumococcal conjugate vaccine (PCV) was procured through the AMC in 2014 alone, a 40% increase from 2013 (58 million doses) and over 3 million children in 6 countries were vaccinated (International AIDS Vaccine Initiative (IAVI), 2008; GAVI, 2015). Country co-financing policies are imperative to help countries recognize these financial challenges and guarantee long-term affordability by pledging room in health budgets for vaccine procurement and delivery. Pooled procurement mechanisms, such as UNICEF's Supply Division and the Pan American Health Organization's (PAHO) Revolving Fund have played important roles in facilitating the adoption of new vaccines and ensuring stable supplies of vaccine at affordable prices (Shiffman & Smith, 2007). In the case of Haemophilus influenza B, pooled procurement strategies were effective in consolidating vaccine orders for economies of scale. This avoided disruption in vaccine supply and guaranteed future funding for vaccine purchase. In an open-label randomized study of the 9vHPV vaccine to both males and females, the children aged 11-15 years either received 9vHPV vaccine concomitantly with diphtheria, tetanus, pertussis, and poliomyelitis vaccine (REPEVAX) or a month after REPEVAX (Kosalaraksa et al., 2015). The concomitant administration of 9vHPV with REPEVAX was well tolerated and did not interfere with the immune response of either vaccine. There were no serious side effects.

2.2.4. Summary

In summary, financing HPV vaccination will require negotiating a cost-effective price with manufacturers, convincing finance and health ministries of the HPV-V's programmatic feasibility, and assuring manufacturers of demand in order to leverage costs and ensure vaccine availability (Saxenian, 2007).

2.3. Mobilizing Public Advocacy and Political Will

2.3.1. Parental Concerns for HPV Vaccine Programs

HPV vaccination is at the intersection of sex, public health and parental rights, has engendered public distrust and a perception of government and industry interference in health and parental autonomy. Reviews of the literature have identified the following parental concerns and barriers to vaccinating their children: the vaccine's effect on sexual behavior, the low perceived risk of HPV infection, social influences, irregular preventive care, mistrust of pharmaceutical companies and government mandates (Holman et al, 2014; Ferrer et al., 2015).

2.3.2. Governmental Concerns for HPV Vaccine Programs

HPV vaccination portrayal by key health officials has not resonated publicly and politically. The number of lives lost to cervical cancer is relatively minimal compared to HIV, TB, Malaria, childhood diarrheal and respiratory illnesses. Additionally the public largely remains unaware of the link between HPV and cervical cancer. Many countries have withdrawn the national support of HPV vaccination. For instance, India suspended HPV vaccination demonstration projects because of public distrust in the vaccine

(Larson, Brocard, & Garnett, 2010). Japan suspended its recommendation that healthy young adolescent girls should all receive the series of three prophylactic HPV vaccination shots following negative media reports regarding purported serious but rare adverse side effects (Ueda et al., 2015). This emphasizes the importance of framing HPV vaccination in a way that resonates with the public agendas (prevention of cervical cancer) as programs can easily be derailed by societal concerns, public emotion and politics (Onder, 2008).

2.3.3 Rwanda's Successful Vaccination Strategy

In 2011, Rwanda became the world's first low-income country to implement universal HPV vaccination. The vaccine was provided through industry donation, with provision for concessional prices for future doses. Careful examination of the public policy framework that led to prioritizing HPV vaccination in Rwanda demonstrates that many of the critical conditions, namely actor power, identification of specific issue characteristics, provided Rwandan health officials the ability to generate political priority and therefore adequately mobilize appropriate financial, technical and human resources for vaccine delivery (Binagwaho, 2012).

"Actor power," encompasses policy community cohesion, which guides institutions and leadership regarding vaccination advocacy efforts. The importance of actor power is highlighted by the MenAfriVac experience in which one month after African Ministers of Health were able to successfully lobby price reduction to $0.50 per dose, over 19.5 million people in Burkina Faso, Mali and Niger were vaccinated (Clark, 2013). Actor Power was instrumental to the propagation of HPV vaccine in Rwanda; Rwanda's First Lady and the Ministry of Health hosted senior Merck officials to initiate advocacy for the HPV vaccine on behalf of women in Rwanda. They worked jointly with Partners in Health to create Rwanda's National Strategic Plan for the Prevention, Control, and Management of Cervical Lesions and Cancer (Africa blog, 2011). This underscores the clear message that vaccine delivery is strongly tied not only to funds but also to the political willpower of key stakeholders. Other sub-Saharan countries have followed suit with endorsements for HPV vaccinations by the ministries of health in Kenya and Uganda (Program for Appropriate Technology in Health (PATH), 2010).

2.3.4 Political Challenges to HPV Vaccine Programs

It is important to address political context as the beneficial effects of HPV vaccination will not be seen for decades. Political agendas frequently focus on short-term gains. Education of governments and political leaders to the long-term importance of reducing the death rate of their women during the prime of their lives is vital for the success of HPV vaccination. The Millennium Development Goals (MDG) have established the political agenda until 2015 and will be replaced with the Sustainable Development Goals in 2016. The SDGs represent a shift in global health goals toward prioritization of equity and provision of universal health coverage. The incorporation of cervical cancer prevention, and specifically HPV vaccination, within this framework allows HPV Vaccine efforts to be seen as congruent to the existing global priority to improve women's reproductive health. Further, there are potential spillover benefits if vaccine delivery is integrated into family planning

and sexually transmitted infections (STI) testing and treatment agendas. Thus, the end of the Millennium Development Goals allows the global public to build consensus on new goals for 2030, creates a space for discourse and allows key t stakeholders to commit to providing access to developing countries (United Nations Development Programs, 2013). The emergence of vaccination as a global priority is largely owed to the lack of cohesion amongst guiding institutions and intergovernmental organizations, civil society and philanthropy. WHO, Save the Children, UNICEF, the US National Institutes of Health, the GAVI Alliance, and the Bill and Melinda Gates Foundations are examples of key stakeholders involved in vaccine prioritization. However, the issues of sexually transmitted infections, HPV, and cervical cancer have largely been treated within the sexual and reproductive health community (SRH). There is a need for a key stakeholder to emerge as the leading HPV Vaccine advocate and to take initial steps to form coalitions within the vaccine community, and to mobilize pediatric and adolescent health and cancer prevention communities in order to prioritize HPV vaccination, address public health concerns and provide guidance on vaccine access and deployment.

2.4 Barrier: Vaccine Infrastructure - Delivery System Challenges

2.4.1 Infrastructure Requirements for HPV Vaccination

Aside from issues of cost and political prioritization, adequate coverage is paramount. Addressing cost and politics scratches the surface of what are important and complicated considerations in order to achieve adequate coverage. Well-designed and implemented vaccine programs can reduce the burden of cervical cancer. The challenges to success include fragile health care systems, the need for school-based programs, and community acceptability. Infrastructure requirements for HPV vaccination include determining the optimal delivery system, identifying the population to vaccinate, and training the appropriate healthcare workers in vaccination strategies (Sankaranarayanan, Anorlu, Sangwa-Lugoma, & Denny, 2013)

2.4.2. Lack of geographic access to care

Areas that bear the greatest burden of cervical cancer are also regions where access to care is limited by lack of road or lack of schools in rural regions (Watson-Jones et al., 2015). Additionally adolescents in crowded slum settlements have lower than average childhood vaccination coverage. For instance, infant slum dwellers in Bangladesh have a 54% vaccination rate compared to the national average (78%) (Uddin et al., 2010).

2.4.3. Linkage with cervical cancer screening

Immunization service delivery is considered the most successful public health system in the world (Kane, Sherris, Coursage, Aguado, & Cutts, 2006). Conversely, current cervical cancer screening remains uncoordinated in many developing countries. Cytology-based screening techniques are established vehicles for significantly reducing the morbidity and mortality from cervical cancer in developed countries but have little traction in developing countries. Inadequate screening and treatment facilities, lack of skilled cytologist and laboratories, and economic costs all play a role in the lack of conventional; screening of this preventable disease (Sangwa-Lugoma et al., 2006). Programs are further limited by poor provider coverage rates and poorer patient follow-up secondary to need for repeat

testing and follow up at referral centers (Franco et al., 2008). Approximately 40-50% of women from developed countries within a given 5-year period have at least one Papanicolaou (Pap) smear, whereas participation is less than 5% in low-income countries (Akinyemiju, 2012). The "see and treat" approach based on visual inspection or HPV-DNA testing followed by cryotherapy is validated screening options (Sangwa-Lugoma et al., 2006). These strategies, while attractive alternatives, face challenges incorporating into existing national cervical cancer prevention programs as well logistic challenges achieving adequate coverage and training sufficient workforce (Tambouret R, 2013). Therefore expanding upon the historical success of immunization campaigns may accelerate goals towards cervical cancer prevention. One option is to link HPV vaccination to cervical cancer screening. One study investigated the feasibility of this linkage in South Africa (Snyman, Dreyer, Botha, van der Merwe, & Becker, 2015). In this study, vaccination rates were 64% and screening rates were 44%. In Sweden, cervical cancer screening was higher in vaccinated women (86%) compared to unvaccinated women (75%) (Herweijer et al., 2015).

2.4.4. Linkage with programs

In almost all the countries, conventional vaccines are delivered through a health delivery system that has been tried and tested over the last several decades. This is promising for HPV since potential incorporation within overall vaccine strategies may facilitate delivery and allow realistic and feasible cervical cancer prevention. What remains to be investigated is an appropriate interface between the health service and educational infrastructures since adolescent females are the primary recipients. In Bhutan for example, HPV vaccination is provided only through a health facility, whereas in the majority of the countries where HPV vaccination is being introduced has been through schools with a catch-up and follow-up through a health facility in the community (Markowitz, 2012). The coverage rates for school-based programs for vaccination are high for high-income countries, such as Belgium and the Netherlands. In contrast, countries without school health facilities to deliver vaccines may simply choose not to implement the vaccine or rely on the health sector. The involvement of schools affords the opportunity to see if related sexual and reproductive health information education, teaching and learning could be strengthened and better synergies harnessed. Programs designed to deliver the vaccine might also provide additional targeted services and health commodities to vaccine recipients, specifically breastfeeding, male/ female condom promotion and multi-visit smoking prevention interventions (Broutet, 2013). Furthermore, targeting schools will lead to incorporation of male vaccination. Studies suggest that the full benefit of cancer prevention will be realized when men are incorporated into vaccination campaigns. Male vaccination will provide sufficient herd immunity to impact community burden of disease (Kim, Andres-Beck, & Goldie, 2007; Yancey, Pitlick, & Forinash, 2010). Another challenge will be achieving coverage in females who have left school, and who likely live in remote areas.

In summary, vaccine delivery faces many barriers. A case study in Tanzania estimated the cost of HPV vaccinations through the school system over a five-year phased implementation. The cost of establishing an HPV vaccine program that delivers three doses of vaccine (at a vaccine price of US $5) to girls at schools would be US $9.2 million (excluding vaccine costs) and US

$31.5 million (with vaccine) (Hutubessy et al, 2012). This study underscores the significant financial and social investment needed for an HPV vaccine program.

3. Safety Concerns

One of the major reasons for stopping national HPV vaccination has been concerns about safety. While careful trials have documented the safety of bivalent and quadrivalent vaccines (Kash et al., 2015), concerns remain. A review of fourteen HPV vaccine studies that assessed safety in low and middle-income countries (LMICs), there were no vaccine-related adverse events (Nakalembe, Mirembe, & Banura, 2015). In an open-label randomized study of the 9vHPV vaccine to both males and females, the children aged 11-15 years either received 9vHPV vaccine concomitantly with diphtheria, tetanus, pertussis, and poliomyelitis vaccine (REPEVAX) or a month after REPEVAX (Kosalaraksa et al., 2015). The concomitant administration of 9vHPV with REPEVAX was well tolerated and did not interfere with the immune response of either vaccine. There were no serious side effects. Nonetheless, data from LMICs on safety and immunogenicity and follow-up is sparse.

4. Conclusion

The aims of this review were to review the barriers to HPV uptake. The Human 394 Papillomavirus (HPV) vaccine has demonstrated effectiveness in the reduction of HPV-associated cervical lesions and is expected to alleviate the global burden of cervical cancer. Thus, the vaccine should be included in national immunization programs, as part of a comprehensive approach to cervical cancer prevention and control; however, significant barriers exist with regards to cost, societal acceptance, and public health advocacy. The practical aspects of vaccine uptake are now the most important issue in HPV vaccine research from a public-health perspective. Increasing uptake, specifically in regions where disease burden is highest, will require thoughtful consideration of cost-effectiveness, innovative financing mechanisms, novel approaches to vaccine vehicle delivery and public acceptance. Paradigms exist, and technological refinement of strategies modeled from other sectors of public health will allow regional adaptation to country-specific circumstances. Only once coverage is universal, are we able to fulfill the promise of HPV vaccination.

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