REVIEW ARTICLE

Human Papilloma Virus Vaccination for Control of Cervical Cancer: A Challenge for Developing Countries

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Abstract

Primary HPV prevention may be the key to reducing incidence and burden of cervical cancer particularly in resource-poor countries. Vaccination programmes are already established in several developed regions, but several grey areas stand in the path of similar success in developing countries. This review sought to identify challenges of HPV vaccination in developing countries and discuss vaccine use, pitfalls and controversies; areas requiring collaborative efforts were identified. A Pub Med search was done; key words included *Human papilloma virus, HPV vaccine* and *sub-Saharan Africa.* Other resources included locally-published articles and additional internet resources. The potential benefit of mass HPV vaccination appears enormous. However, the challenges of competing health demands, poverty, ignorance, religion, culture, weak health system, establishment of an effective intersectoral collaboration and underfunding must be overcome to make maximal vaccine uptake a reality. Education and effective communication is crucial in achieving successful immunization programmes (*Afr J Reprod Health 2011; 15[1]: 25-30).*

Résumé

Vaccination contre le virus du papillome humain pour le contrôle du cancer du col : Défi pour les pays en développement. La prévention du virus VPH peut être la clé à la réduction de l'incidence et du fardeau du cancer du col, surtout dans les pays qui n'ont pas assez de ressources. Des programmes de la vaccination ont été établis dans plusieurs régions avancées, mais beaucoup d'incertitude entravent le succès pareil dans les pays en développement. Cette étude a cherché à identifier les défis de la vaccination contre le VPH dans les pays en développement et discute l'emploi du vaccin, les pièges et les controverses ; les domaines qui méritent les efforts en collaboration ont été identifiés. Nous avons fait une recherche à la Pub Med ; les mots clé comprenaient *le virus papillome humain, le vaccin contre le VPH* et *l'Afrique subsaharienne*. D'autres ressources comprenaient les articles publiés localement et des ressources d'internet supplémentaires. L'avantage potentiel de la vaccination contre le VPH paraît énorme. Néanmoins, les défis des exigences sanitaires qui se font concurrence, la pauvreté, l'ignorance, la religion. La culture, un système sanitaire peu efficace, l'établissement d'une collaboration intersectorielle efficace et l'entente doivent être maîtrisés pour rendre l'acceptation du vaccin maximal une réalité. L'éducation et une communication efficace sont cruciales pour accomplir des programmes de l'immunisation réussite (*Afr J Reprod Health 2011; 15[1]: 25-30).*

Keywords: Human papilloma virus, HPV vaccine

Introduction

The human papilloma virus (HPV) has been recognized as a major aetiological agent in anogenital intraepithelial neoplasia (AGIN)—precursors of cancers of the vulva, vagina, cervix, penis and anus[1]. Over 200 HPV serotypes have been identified and at least 40 are specific to the genital tract. The importance of the HPV is evident in the pathogenesis of invasive cervical cancer (ICC) where it has been found in 99.7% of cervical cancer cases worldwide [1,2].

Cervical cancer screening using the traditional Papanicolau smear and liquid-based cytology (LBC) has been pivotal in the decline in incidence and mortality rates from this disease in developed countries[3]. The situation has been further strengthened with the development and deployment of vaccines against specific HPV serotypes as a form of primary prevention with evidence of immense potential[4,5]. The burden of cervical cancer, difficulties with secondary prevention and deployment of screening and treatment frameworks on a nationwide basis in resource poor countries suggest that HPV vaccination may be a veritable strategy.

Epidemiology

HPV infection is particularly common in the first few years following sexual contact with estimated prevalence rates of 25-40% in women up to 20 years of age and 10% in women above 40 years[1]. In the US, it is one of the commonest sexually transmitted infections (STIs) with 6.2 million new infections annually and a 50-80% lifetime risk of infection in sexually active women[6,7]. In Nigeria, the estimated incidence rate of ICC is 25 per 100,000 women and about 8000 new cases of cervical cancer are diagnosed in the country each year[8]. The age-standardized prevalence rates of HPV infection outside sub-Saharan Africa ranges from 1-15%[9]; Thomas et al. found a rate of 25.6% among women with normal cytology in Nigeria [10].

Transmission of the virus is predominantly by sexual contact (penetrative or non-penetrative); other routes have lesser

significance[11, 12]. Other factors that modify the risk for infection include the Human Immunodeficiency Virus (HIV), smoking, multiparity, long term use of oral contraceptive pills and other sexually-transmitted infections like Chlamydia spp, and Herpes simplex virus[12]. HPV serotypes are subdivided into high (hrHPV) and low risk (lrHPV) according to their propensity for benign or malignant lesions. Serotypes 6 and 11 are the commonest lrHPV types and are responsible for 90% of genital warts[1, 13].

Infection with multiple serotypes has been found in 20-30% of women worldwide and distribution varies between different geographical locations[13]. HPV 16 and 18 are the commonest hrHPV types, found in 70-84.3% of ICC in Europe and North America and 66.8% in sub-Saharan Africa[1, 12, 13]. HPV 45 has also been found in 14%-15% of cases in sub-Saharan Africa[14, 15]. ICC continues to cause much more devastation in developing countries where at least 80% of cases are found [16]. The perennial contributory factors include late presentation, non-existence of screening programmes, insufficient resources for treatment and lack of trained personnel.

HPV Vaccination: Principles, Development and Current Formulations

The HPV vaccines are the first group of vaccines developed to prevent cancers caused by a virus [17]; they stimulate development of an immune response that prevents persistent infection and eventually genital cancer. The risk of multiple infections is heightened by the presence of multiple serotypes and, therefore, the ideal vaccine would protect against every existing type with potential for AGIN or invasive genital cancer. The perfect time of delivery would therefore be before sexual debut.

There are two classes of vaccines—prophylactic and therapeutic. Existing prophylactic vaccines are bivalent (Cervarix®) or quadrivalent (Gadarsil®). Cervarix® protects against HPV serotypes 16 and 18, while Gadarsil® protects against serotypes 6, 11, 16 and 18. Specific therapeutic vaccines are still in development and are expected to attack already-established HPV infection and HPV-related disease. Prime-boost regimens with enhancement through therapeutic viral vector vaccines appear to be an effective approach[18]. Non-specific immunotherapeutic medications such as imiquimod and cidofovir act as immunomodulators and antiviral agents; use of these agents is limited to clinical trials with small numbers of women[1, 19, 20]. Current vaccines were developed as a solution to the difficulties with producing the virus in continuous culture. To surmount this problem, virus-like particles (VLP) were produced from the L1 capsid protein and utilized to produce a significant immune response due to morphological similarity with the actual virus[19].

Results from trials using prophylactic vaccines show almost total protection against new and persistent infections in comparison with placebo [4, 5, 19]. Investigators from the FUTURE (Females United to Unilaterally Reduce Ecto/Endocervical Disease) II study found a 98% protection from HPV 16 and 18 after 3 years of follow up [4]. The primary end point was CIN II, III or carcinoma in situ. The presence of cross-protection has also been confirmed by evidence of protection from HPV 45 when the bivalent vaccine is administered[21]. Another study suggests that these vaccines will also stem the observed rise in adenocarcinomas of the cervix; this histological type is usually more difficult to detect using the Pap smear as it arises from the endocervical glands [22].

Gadarsil® was approved for use by USA's Food and Drug Administration (FDA) in June 2006 and is recommended for 11-12 year old girls (who are expected not to have been sexually exposed). Females aged 9-26 years may also be vaccinated. Initial evidence was insufficient to support its use in pregnancy and in women above 26 [23], but more recently, it has been demonstrated to be efficacious-s in women aged 24–45 years not already infected with the relevant HPV types [24]. Cervarix® on the other hand, is licensed for use up to 45 years in Australia [25]; an immunogenicity study of bivalent vaccine showed 100% seroconversion in women up to the age of 55 years [26]. Vaccination has also been suggested for males in order to reduce morbidity from penile, head, neck and anal cancers and as a means to increase herd immunity [27]. Current guidelines suggest that boys and men aged 9 through 26 years may also receive the vaccine [28]. In terms of cervical cancer prevention, however, mathematical modelling suggests that it is more cost-effective to focus resources on vaccinating as many girls as possible, rather than vaccinating both girls and boys [29].

Adverse effects, according to the FUTURE II study [4], were minimal and included pain, erythema, fever and swelling at the injection site; serious adverse effects were found in 0.7% of patients. Concerns have been expressed following other reports of serious adverse effects ranging from paralysis to death [30]. This was sufficient to raise strong opposition to mandatory use as proposed by some states in the US [31]. The FDA has however stated that adverse effects reported to its Vaccine Adverse Event Report System (VAERS) may be casual, rather than causal and cannot be interpreted as such—however, post-licensure safety surveillance continues [32, 33].

Despite the efficacy that has been observed with the prophylactic vaccines, some limitations have been observed. These vaccines do not protect against all the serotypes responsible for cervical cancer. For now, the use of HPV vaccines does not obviate the need for continued screening and secondary prevention using various methods including the Pap smear, visual inspection and colposcopy; and it is yet to be determined if booster doses will be required. The exact duration of antibody protection is unknown, although the longest follow-up study so far has shown high (up to 11- to 13-fold above natural infection levels) antibody levels up to 7.3 years after vaccination with Cervarix® [34]. Statistical models also predict that Cervarix® will provide antibody levels well above that of natural infection for at least 20 years [35].

A Panoramic View at Issues in the Developed World

In developed countries, significant progress in the introduction of HPV vaccination programmes has been made; licensure and approval has been obtained in over 100 countries with 28 high resource nations including HPV vaccines in their national immunization schedule. In most of these nations, the issues have revolved around safety and adverse effects, permissiveness of sexual debut in pre-pubertal girls and increased rates of unprotected sex in adolescents [36]. Other issues include insufficient awareness and information among relevant health workers [37] especially paediatricians, whose patients are the targets, even though they often do not see or treat the sequelae of HPV infection [38].

For the developed world, education, advocacy, acceptance and evaluation of long-term vaccine efficacy appear to be

crucial to increasing uptake of the HPV vaccine. Secondary prevention of cervical cancer is already well established in Europe and Scandinavia [39] with an increase in the use of HPV testing for triage of women with suspicious lesions. There are segments of the populace in high resource nations that are convinced that the HPV vaccine is harmful to recipients and despite reports from policy makers, the controversy continues to rage [30]. In the developing countries however, there is a much bigger picture to consider.

HPV Vaccination—Challenges in Developing Countries: *The Existing Immunization Framework*

Vaccine delivery in developing countries involves both public and private sectors. The public sector essentially benefits from national immunization programmes in collaboration with the World Health Organization (WHO)'s Expanded Programme on Immunization (EPI). It is recommended that new vaccines are introduced via existing frameworks [40]. Unfortunately, despite efforts of policy makers and donor agencies, several countries in Africa still have suboptimal immunization coverage [37]. With the present frameworks in the African continent, policy makers will have to make key decisions regarding the necessity of the HPV vaccine and the availability of local resources and personnel for campaigns.

WHO recommends that routine HPV vaccination should be included in national immunization programmes, provided that prevention of cervical cancer or other HPV-related diseases, or both, constitutes a public health priority; vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost effectiveness of vaccination strategies in the country or region is considered [41]. With respect to developing countries, where there may be no facilities for well-child health care, WHO recommends evaluation of the immune response to vaccine at school entry (when contact with girls would be much easier than in later years) and in infancy (as part of the routine immunization schedule), and evaluation of simultaneous administration of HPV vaccine with these routine vaccines [42].

Funding and cost implications

There is still a significant dearth in investment by pharmaceutical companies in vaccines and immunization. An estimated 1.7% of funds were spent on vaccines in 2002 [43]. Despite the efforts of the Vaccine Fund, the Global Alliance for Vaccines and Immunization (GAVI)—consisting of the United Nations Children Fund (UNICEF), the WHO, World Bank, Bill and Melinda Gates Foundation and other private philanthropists, donor and implementing country governments, non-governmental organizations (NGOs), public health specialists, vaccine industry representatives, the financial community—and other sources of funding, it may not be sufficient to cope with the estimated total vaccine costs of USD 14-30 billion and about 109 million females who will require immunization [43].

In several low resource countries, diseases such as malaria, polio, diphtheria and tetanus constitute 'unfinished business' and remain considerably important. Evidence suggests that majority of 'late adopters' of vaccines would be developing countries and it remains to be seen if these countries will have sufficient political will to incorporate HPV vaccination into the health system due to competition for scarce resources. It is important that advocacy also focuses on preparation of the health sectors of developing countries, particularly in sub-Saharan Africa for cost implications of an additional vaccine. This will enable preparation for existing demand, capital and recurrent costs including vehicles, cold chain equipment, training, transportation, personnel and communication [44]. GAVI has prioritised support for HPV vaccines as part of its new vaccine investment strategy—a strategy which identified the vaccines that would have the biggest impact on the disease burden in developing countries [29].

Religion, culture and misconceptions

Religious groups in the developing world are likely to view HPV vaccination with caution and some conservative groups may reject the vaccine outright. A major concern is the potential that it would amount to a license to have sex and undermine the abstinence movement. Suspicions of the West are considerable—in 2003, opinion leaders in Kano, Nigeria shut down an effort to immunize children against polio amidst rumours that the vaccine would result in sterilization or that it contained HIV [45].

`Conspiracy theories are of particular concern in HPV vaccination because of the involvement of pre-adolescent girls [45]. Education of parents, care givers, religious leaders and policy makers will be required to allow these groups to make informed choices. It will not be sufficient to inform these groups about the benefits of the vaccine; it will be necessary to clearly define what the vaccine protects against and what the vaccine cannot be expected to achieve at this time [46].

Education and communication

For women in developing countries, a major source of information for this new vaccine will be their physician or gynaecologist. However, studies suggest that the health care workers also have insufficient information to guide and counsel parents and adolescents[46]. To enable proper dissemination of facts about the HPV vaccine, workshops, conferences and continued advocacy by public health physicians with the assistance of donor agencies and the WHO will be crucial. Usually, opposition is the result of insufficient or poorly managed information. Successful education of the general populace will require continued education about the preventable nature of carcinoma of the cervix, the need for continued screening despite the vaccine, cost of the vaccine and details of vaccine efficacy and side effects.

Vaccine efficacy

It remains crucial to determine the long term effects of vaccination for HPV; it is also important to determine sero status in vaccinated individuals and whether booster doses would be needed in future [47]. Current methods for determining antibody levels require highly specialized laboratories and are expensive. Without collaboration with and assistance from health and donor agencies, it may be difficult to monitor the efficacy of these vaccines in developing countries over the long term.

Africa and the HPV Vaccine: The Story So Far

The African continent continues to bear the consequences of its significant cervical cancer burden. Progress in vaccination awareness and programmes has remained slow. In March 2007, Uganda was included in the PATH pilot study for HPV vaccination [48]. In Nigeria, the 1st Stop Cervical Cancer In Africa meeting was held in July, 2007; organized by an NGO—Princess Nikky Foundation. The need for support for mass screening for cervical cancer and advocacy for the HPV vaccine was emphasized [49]. As part of efforts by the Nigerian government to reduce disease burden from cervical and other cancers, the former First Lady was successful in raising funds for an International Cancer Centre [50]. In addition, a cervical cancer control policy is being developed and the two vaccines have been registered. Glaxo Smith Kline, in a tiered pricing scheme, has presently begun marketing of its bivalent vaccine (Cervarix®) in Nigeria at 50% of its usual price [51].

Recent findings from the Evidence for Impact project have confirmed that with adequate delivery, advocacy and communication strategies, successful vaccination programmes can be achieved in developing countries [52,53]. The findings from these pilot projects have been followed up by recommendations for HPV vaccination in sub-Saharan Africa [54]. Key statements in these guidelines include immunization of females aged 9-12 years as part of school based or community based immunization programmes. It has also been stated that women above 26 years should be given the opportunity to discuss usefulness of immunization with their provider.

It has been recognized that mass immunization involving rural areas (populated by approximately 70% of people) may be cost-effective in the long term. However, the main challenge for now appears to be the implementation of effective multi-sectoral collaboration (including communities, health professionals, NGOs and faith-based organizations) and meandering around obstacles posed by the high cost of immunization [49, 55].

Conclusion

The burden of cervical cancer in Africa remains high. Since the aetiology of cervical neoplasia is incontrovertibly linked to persistent oncogenic HPV, there is enormous potential in mass vaccination, especially against high risk types. However, the challenges of competing health demands, poverty, ignorance, religion, culture, weak health system, establishment of an effective intersectoral collaboration and underfunding must be overcome to make maximal vaccine uptake a reality. Education of stakeholders, effective communication and training of all physicians in general practice, paediatrics, public health and obstetrics and gynaecology is crucial to ensuring acceptance and participation in immunization programmes.

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