Cervical Cancer Vaccination

Abioye R Ajiboye
*Carnarvon Regional Hospital WA 6701 Australia. Formerly, Department of Obstetrics & Gynaecology, University of Ilorin Teaching Hospital, Nigeria.

Abstract
Background: In 2006, the world's first cervical cancer vaccine became available for public use. Two human papilloma virus (HPV) vaccines, Gardasil & Cervarix were licensed, both protecting against the most common cancer-causing HPV types (HPV 16 and 18), and Cervarix also protecting against genital warts (including in addition, types 6 and 11). A good understanding of the vaccine, its role in the primary prevention of cervical cancer and pre cancers is vital in reducing the high morbidity and mortality associated with cervical cancer.
Objective: This article provides an overview of cervical cancer vaccine including safety, efficacy and cost in the primary prevention of cervical cancer.
Discussion: The quadrivalent human papilloma virus (HPV) vaccine protects against HPV types 6, 11, 16 and 18. These HPV types are responsible for 70% of cervical cancers, 90% of genital warts and a substantial proportion of cervical abnormalities. The quadrivalent human papilloma virus (HPV) vaccine is indicated for females aged 9 -26 years and males aged 9-15 years and should ideally be administered before the onset of sexual activity, however, sexually active patients will also benefit. These vaccines are expected to be able to prevent about 70% of cervical cancer cases worldwide
Keywords: Human Papilloma Virus, Vaccine, Immunization

Introduction

More than ever in history, vaccines in this century promise to be the first and best line of defence against disease. With the availability of human papilloma virus (HPV) vaccine, primary prevention of both

Precancerous and cancerous cervical lesion is now possible[1]. Together, screening and vaccination will potentially further reduce the enormous burden of cervical cancer worldwide. Human papilloma virus is the most common viral infection of the reproductive tract worldwide often regarded as the common cold virus of the genital tract and infects an estimated 660 million people[2]. While HPV infection resolves spontaneously in the majority of people, it can develop into chronic infection and, in some women, into cervical cancer. The peak incidence of HPV infection occurs in adolescents and young women, while cervical cancer typically follows 20–30 years later. The five most common HPV types in squamous cell cervical Carcinoma vary to some extent in different regions of the world. In all regions, types 16 and 18 are the most common, together accounting for 73.5% of cancers in Asia, about 65% in Africa and central/south America, and 71.5% in Europe and the United States. The next most common genotypes include types 45 in Africa and Asia; 31 in Latin America, 33 in Europe and North America and 58 and 52 in Asia[2, 3]. In many developing countries, awareness of the role of HPV in cervical cancer is low even among physicians and other health professionals[2, 4, 5].

Worldwide, cancer of the cervix continues to be the second commonest female cancer and affects approximately 1.4 million women with more than half a million new cases and half of these die as a result every year. The highest incidence rates are observed in sub-Saharan Africa and Latin America [2, 6]. The disease represents a major

health inequity, as 90% of those with cervical cancer live in developing countries. Though, Cervical cancer is a preventable disease yet invasive cervical cancer remains the most common cancer in the developing countries and the second leading cause of cancer mortality in women due to poor prognosis attributed to lack of awareness about the disease and its prevention, late presentation in advanced stage when cure is unrealistically impossible with overburden of the limited and inadequate facilities, ineffective cervical cancer screening programme, dearth of women education and empowerment[2,7,8,9]. India recorded over 130 000 new cases of cervical cancer in 2002 and accounted for approximately 25% of the world's burden of cervical cancer. The exact burden of cervical cancer in Nigeria remain unknown but of public health significance. The high incidence of invasive cervical cancer rates in Nigeria reflects an inactive national cervical Pap screening program. In Ilorin, Nigeria 62.3% of gynaecological cancers were histologically confirmed primary cervical cancers[9]. The link between sex, human papilloma virus infection and cervical cancer has long been established. Marriage, sexual activity, multiple sexual partners or cohorts, increase in parity are epidemiological determinants of cervical cancer.

Before the introduction of cervical screening programmes in the 1960s and 1970s, the incidence of cervical cancer in developed countries was similar to what obtain in developing countries today. Incidence rates are now low in developed countries, but this pattern is relatively recent. Industrialized countries have greatly reduced deaths from cervical cancer through effective screening programmes that allows early detection and treatment. These programmes are inactive, expensive and difficult to implement in low-income countries.

Human Papilloma Virus (HPV)

Overview

Human papilloma virus is a common virus that affects both males and females. HPV is now universally recognised as a necessary agent for the development of cervical cancer with HPV being present in 99.7% of cervical cancers[3]. The virus is also associated with over 90% of genital wart cases, approximately 70% of anal cancers, approximately 50% of penile cancer lesions, and approximately 20% of oropharyngeal cancers[3]. HPV16 and HPV18 account for 70% of cervical cancers but infection only rarely leads to cancer (<2%) with a15 year lag period between infection and cancer[2]. Up until now, detection of precancerous cervical lesions was the key to preventing cervical cancer through regular gynaecological screening programmes that allow early detection and treatment of precancerous lesions. In developing countries, however, this method has had only a limited impact due to the cost and complexity of properly screening and treating women. In a study from a tertiary health institution in Nigeria, only 5.2% of female health workers had had previous Pap smear[5]. There are over 100 HPV subtypes including 40 anogenital types with some 15 high risk (oncogenic) types such as HPV 16, 18, 31 and 45 conferring cervical cancer risks. High risk HPV types are found in different proportions throughout the world; however HPV 16 and 18 are responsible for at least 70% of cervical cancers and 50% of high grade lesions worldwide[1, 2, 6]. Low risk subtypes such as 6 and 11 are involved in greater than 90% of genital warts and approximately 10% of low grade cervical abnormalities[1,2] (Table 1)

Natural History of Human Papilloma Virus (HPV)

Human papilloma virus is a non enveloped double stranded circular DNA virus. The virus is highly infective with transmission rates of over 50% following exposure to a person

Table 1. Effects of HPV Infection in Women & Men

HPV type	Women	Men
16/18 (High risk subtypes)	• 70% of cervical cancer2 • 50% of CIN 2/36 (HSIL) • 25% of CIN 17 (LSIL) • Most anal cancers2	• Most anal cancers2 • Potentially prevention of Infection (reduced Transmission on to Women)
6/11(Low risk Subtypes)	• 10% of CIN 112 • >90% of genital warts10	• Potentially prevention of infection(reduced Transmission on to Women) • >90% of genital warts10

with productive anogenital HPV infection[13]. The highest prevalence of HPV infection has been identified in sexually active women 25 years of age and younger. Up to 80% of sexually active women and men will be exposed to at least one type of HPV in their lifetime. Most people get their first type of HPV infection within their first few years of becoming sexually active. While the infection is so easily passed on, more than 90% of infections are cleared by the body immune system within the first two years[13].Infection with the anogenital types occurs largely through any type of genital contact and not necessarily genital penetration. Condoms can reduce transmission, but do not prevent infection. Condoms does not offer complete protection against HPV infection as it is transmitted through genital skin contact[3],Human Papilloma virus enters the body through micro abrasions in the anogenital skin and replicates in the basal epithelial cells. Infection is often subclinical but may present as condyloma (warts), cervical or anogenital abnormalities and cancers. Most women who contract HPV infection clear it spontaneously within a median of 8–14 months with persistence of a high risk HPV type only occurring in 3–10% of women. Persistent HPV infection is a key biological intermediate in cervical carcinogenesis. Low grade squamous epithelial lesions (LSIL) seen on Pap smears reflect acute infection with HPV and regression occurs in most cases. Much of the burden of this low grade disease occurs in young women. High grade squamous intraepithelial lesions (HSIL) as noted on Pap smears probably represent viral persistence and integration of HPV DNA and require treatment. Progression of these lesions and the development of invasive squamous carcinoma of the cervix can occur over time. In Nigeria, approximately 80% of these high grades cervical abnormalities occur in women under the age of 40 years[14]Procedures to remove these lesions are associated with increased risk for adverse pregnancy outcomes[15].

Development of Human Papilloma (HPV) Vaccine

Vaccination aims to produce neutralising antibodies capable of preventing infection by binding tightly to the surface of the virus and physically preventing the virus from docking with, and attaching to, a host cell. Human papilloma virus capsid structural proteins are the logical target for such antibodies, but HPV itself has been notoriously difficult to artificially culture. The landmark discovery of the 'late' capsid proteins 'L1' is widely recognised as leading to the development of the HPV vaccine. Australian research team at the University of

Queensland led by Professor Ian Frazer, and Dr Jian Zhou, identify the VLPs. L1 assembles to form empty capsids, known as virus-like particles (VLPs) when expressed in yeast or other cells. VLPs contain no infectious genetic material and because they are recombinant proteins have no oncogenic or disease causing potential, therefore being ideal for use as vaccines. The quadrivalent HPV vaccine contains highly purified VLPs of the major capsid protein (L1) of the HPV types 6, 11, 16 and 18. The VLPs mimic the shell of the virus and are capable of generating potent antibody responses[2].

The HPV vaccines are developed from DNA-free virus-like particles (VLPs) synthesized by self-assembly of fusion proteins of the major capsid antigen L1. Cervarix vaccine is a quadrivalent vaccine containing L1 VLPs of types 6, 11, 16 and 18 expressed in S. cerevisiae yeast. Inclusion of types 6 and 11 in a prophylactic vaccine is expected to prevent more than 90% of cases of genital warts and to protect against the early cervical dysplasia seen with types 6 and 11. Gardasil vaccine contains VLPs of types 16 and 18 and is based on recombinant baculovirus technology. These vaccines are expected to be able to prevent about 70% of cervical cancer cases worldwide, among women who have not yet been infected with HPV of high-risk types (to date, there are no sufficient data regarding prevention of cancer among women who have already experienced an infection). The prevalence of types 16 and 18 varies between countries, however, and the coverage would be slightly lower (around 65%) in Latin America and sub-Saharan Africa. A vaccine that included the seven most common HPV types worldwide (16, 18, 31, 33, 45, 52, 58) is predicted to be able to prevent 87% of all cases, with little regional variation. As of the end of 2006, the vaccine had been approved in 49 countries worldwide, with more expected to join the list in later years[2]. From April 2007, Australian introduced free National human papilloma (HPV) vaccination program to females aged 12 to 26 years.

Efficacy of Human Papilloma (HPV) Vaccine

Efficacy trials for the quadrivalent HPV vaccine included two randomised, double blind, placebo controlled trials – FUTURE I and II. In these studies 5746 and 12 157 women aged 16 to 26 years respectively, were evaluated in 33 countries.[1] The clinical trials did not exclude women with evidence of HPV infection. Of the approximately 20 000 mostly sexually active women enrolled in the phase II and III clinical trial program, 73% were naïve to all four vaccine HPV types before vaccination.[1]

After a follow up of approximately 2 years (on average) among women who were naive to the relevant HPV types before vaccination, the efficacy of the quadrivalent HPV vaccine was 100% for the prevention of HPV 16 or 18 related cervical intraepithelial neoplasia (CIN) grade 2 or worse or AIS (adenocarcinoma in situ), 95% efficacy for the prevention of CIN (any grade) caused by HPV 6, 11, 16 or 18 and 99% efficacy for the prevention of external genital lesions (genital warts and vulvar or vaginal intraepithelial lesions) due to the vaccine HPV types.[1,16]

Evidence of efficacy was observed to commence during the vaccination period.

The vaccine is best administered before the onset of sexual activity and therefore before potential infection with HPV, however, sexually active women also stand to benefit from vaccination. In women with previous HPV infection, as indicated by the presence of either antibodies or HPV DNA in samples at baseline, the vaccine was effective in preventing disease due to the remaining HPV types (to which they were naïve). Among women seropositive or DNA positive to one or more of the vaccine HPV types, the vaccine was 100% effective against CIN 2 or worse or AIS due to the remaining HPV types.

The vaccine was also highly effective against external genital lesions.14 Currently, efficacy data to 5 years is available from the phase II trials, where the combined incidence of HPV 6,11, 16, and 18 related persistent infection or disease was reduced in vaccine recipients by 96%.[15] The overall efficacy of quadrivalent HPV vaccine will depend on the baseline prevalence of HPV infection and disease in the population vaccinated.[1] This is because the quadrivalent HPV vaccine has not been shown to protect against the consequences of all HPV types and will not protect against established disease caused by the HPV types contained in the vaccine.

Immunogenicity

The quadrivalent HPV vaccine appears to be highly immunogenic. Over 99.5% of subjects became seropositive to all four HPV types by one month after the third dose. Antibody levels induced by the vaccine were substantially higher than those observed in women with evidence of natural HPV infection and a subsequent immune response.[1]Antibody levels in males aged 10–15 years and females were significantly superior to that observed in those aged 16–23 years. Immunogenicity data has been used to link efficacy in females 16–26 years to the younger populations.[1] Antibody response appears prolonged and evidence of an immune memory response has been observed.[17]Sentinel cohorts have been set up to evaluate long term efficacy well in advance of the general population. The need for booster vaccination is not yet established, although long term protection is anticipated. Other similar models such as hepatitis B vaccination,[18]give confidence for long term protection.

Vaccination Target Group

The quadrivalent HPV vaccine is registered for use in females 9–26 years of age and males aged 9–15 years.[1] Vaccination will benefit all patients within this age group with the greatest benefit being derived if administered before the onset of sexual activity. Even if a patient has been sexually active and infected with one of the four types in the quadrivalent HPV vaccine, they will still benefit from vaccination against the other three. In clinical studies of the women who had been infected with at least one vaccine HPV type, most were infected with only one type1 Therefore sexually active women should not be discouraged or excluded from vaccination.

It is important to note, HPV vaccination is not a substitute for a Pap test and women should be instructed to continue with regular screening as not all oncogenic or high risk types are covered by the current vaccine. In addition, vaccination is not a treatment for existing HPV related disease – it is preventive of infection with four HPV types. Efficacy studies are ongoing in men and older women with data likely to be available in 2–3 years.

Protocol for Vaccination

The quadrivalent HPV vaccine is available as a pre filled syringe for ease of use. Each 0.5 ml dose contains approximately 225 µg of aluminium adjuvant. It should be administered intramuscularly in three doses of 0.5 ml, at 0, 2 and 6 months. It is generally considered to be best administered at the age of nine to 13 years, before girls become sexually active and potentially exposed to HPV. However, in clinical studies efficacy has been demonstrated in individuals who have received all three doses within 1 year. If an alternative vaccination schedule is necessary, the second dose should be administered at least 1 month after the first dose and the third dose should be administered at least 3 months after the second dose.[1] Concomitant administration of quadrivalent HPV vaccine with hepatitis B vaccine has been demonstrated as safe and as immunogenic as when injections are given separately.[1] Partnership between health programmes is vital for a coordinated

introduction of the vaccine, and to deliver other interventions while immunizing against HPV. It's important to make sure that HPV vaccine is available globally especially for females at risk in developing countries through concerted efforts of national and international organizations. The vaccine is also on the WHO prequalification list, which could open the door to purchases in developing countries via United Nations agencies[2]

Side Effects and Safety

In clinical trials, quadrivalent HPV vaccine demonstrated a favourable safety profile when compared with placebo. Few subjects (0.2%) discontinued due to adverse experiences. Local symptoms such as injection site reactions (pain, swelling, and erythema) were reported. The majority of patients (94.4%) who received the vaccine judged their injection site reaction to be mild or moderate in intensity. Fever has also been reported.[1] Approximately, 10% of participants in the FUTURE studies became pregnant and were instructed to defer completion of the vaccination regimen until resolution of the pregnancy. Outcomes of these pregnancies were comparable in subjects who received placebo and subjects who received the quadrivalent HPV vaccine. However, women should not electively vaccinate if pregnant. The quadrivalent HPV vaccine has been designated Category B2status in pregnancy. There is no contraindication to the use of the vaccine during lactation.1 Normal precautions such as not vaccinating during a moderate to severe febrile illness and inquiry into hypersensitivity to yeast or other vaccine component(s) should be followed.1

Cost Implications

Globally, the primary aim of HPV vaccination will be to prevent cervical cancer. Human papilloma virus (HPV) vaccines have the potential to be a more practical and cost–effective way to reduce the incidence of cervical cancer. However, cost is a major barrier to making the vaccine widely available especially where it is most needed. Current price of approximately US$ 90 a dose for a three-dose vaccination schedule make the vaccine expensive and unaffordable but still far cheaper than the morbidity & mortality cost of cancer of cervix even in the poorest countries. It's expected to become cheaper and widely available in the nearest future.

Strategy for Cervical Cancer Vaccination in Nigeria

Cervical cancer is the leading cause of morbidity and mortality of all malignancies in Nigerian women. Collaborative and concerted efforts by government, women and professional organisations and individuals will be needed to combat a potentially preventable sexually transmitted cancer. A well focused political will by government is central to a cervical cancer vaccination as part of a comprehensive reproductive health package. Professional organisations such as SOGON would be required to work with bodies with similar interest in the areas of research, policy formulation & implementation of reproductive health issues and formulating a sexual health education package for adoption in all schools. Nigeria needs to introduce a school vaccination programme targeted at girls at entry to secondary school for simultaneous administration of HPV vaccine with tetanus toxoid, measles, mumps and rubella vaccines. The vaccine should be funded for females aged 12–26 years. The National Immunisation Program should be repackaged to achieve immunisation of Nigerian children where they live to reduce the overall disease burden. While support of international agencies would still be needed to make the vaccine affordable and available, it will remain an illusion to continue to depend on

donor agencies to improve the health status of Nigerians. Screening and treatment services for cervical cancer will still be required as the vaccines only prevents about 70% of cervical cancer cases and it would be years, if not decades, before the full benefit of vaccination in terms of a reduction in the incidence of cervical cancer occurs. Female education and women empowerment remain core and pertinent to enhance reproductive health in Nigeria.

Conclusion

Human papilloma virus vaccination presents a paradigm shift in the management of cervical cancer. Combined with cervical screening, vaccination will provide women with their best chance of protection against cervical cancer and cervical abnormalities. The quadrivalent HPV vaccine is indicated for females aged 9–26 years and males aged 9–15 years and should ideally be administered before the onset of sexual activity, however sexually active individuals will also benefit.

Summary of Important Points

- The quadrivalent HPV vaccine protects against HPV types 6, 11, 16 and 18.
- HPV types 16 and 18 cause 70% of cervical cancer cases and 50% of high grade cervical abnormalities.
- HPV types 6 and 11 cause 90% of cases of genital warts and approximately 10% of low grade cervical abnormalities.
- Vaccination is indicated for females aged 9–26 and males aged 9–15 years.
- Best time to vaccinate: the sooner the better – ideally before onset of sexual activity, although sexually active women will also benefit.
- Women should continue with regular Pap tests as not all oncogenic or high risk types are covered by the vaccine.
- Vaccination is not a treatment for existing HPV related disease – it is preventive of infection with four HPV types.

References

1. *Gardasil Product Information TGA Approved* June 2006. Available at www.cervicalcancer.com.au/healthprofresources.asp [Accessed 31 March 2007].
2. World Health Organisation. April 2005. *Report of the Consultation on Human Papillomavirus vaccines*. Available at www.who.int/vaccinesdocuments/DocsPDF05/816screen.pdf [Accessed 29 March 2007].
3. Walboomers JMV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999;189:12–9.
4. Peter O. Adefuye, Olabisi Onabanjo University Teaching Hospital, Sagamu, Ogun State, Nigeria Knowledge and practice of cervical cancer screening among female professional health workers in a sub-urban district of Nigeria *Nigerian Medical Practitioner* Vol. 50(1) 2006: 19-22
5. Udigwe GO: Knowledge, attitude and practice of cervical cancer screening (pap smear) among female nurses in Nnewi, South Eastern Nigeria. *Nigerian Journal of Clinical Practice* Vol. 9(1) 2006
6. Shafi MI: Premalignant and malignant disease of the cervix In: Keith Edmonds(ed), *Dewhurst's Textbook of Obstetrics and Gynaecology for Postgraduates, 6th edition*, Blackwell Scientific pub. Pp 572-581.
7. Ijaiya MA, Aboyeji PA, BuhariMO: Cancer of the cervix in Ilorin,Nigeria. *West African Journal of Medicine* Vol.23(4) 2004: 319-322
8. Airede LR ,Malami SA: A five-year review of female genital tract malignancies in Sokoto, Northwestern Nigeria. *Mary Slessor Journal of Medicine* Vol. 5(1), 2005: 51-56
9. Ijaiya MA, Aboyeji AP, Olatinwo AWO, Buhari MO: Clinico-pathological presentation of primary cervical cancer seen in Ilorin, Nigeria. *Nig. J. of Surgical Research* Vol.4(3-

4) 2002: 89-93
10. Clifford GM, Rana RK, Franceschi S, et al. Human papillomavirus genotype distribution in low grade cervical lesions: comparison by geographic lesions and with cervical cancer. *Cancer Epidemiol Biomarkers* Prev 2005;14:1157–64.
11. Jimoh AS, Abdul IF: A Review of One Hundred and Three (103) Histologically Confirmed Cases of Carcinoma of the Cervix at the University of Ilorin Teaching Hospital, Ilorin, Nigeria. *Nigerian Medical Practitioner* Vol. 45 No 4, 2004(56-60)
12. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, et al. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. *Lancet* 2006;367:489–98.
13. Banatvala JE, Van Damme P. Hepatitis B vaccine: do we need boosters? *J Viral Hepat* 2003;10:1–6.
14. Villa LL, Costa RLR, Petta CA, et al. Induction of immune memory following administration of a prophylactic quadrivalent human papillomavirus (HPV) types 6/11/16/18 L1 virus-like particle (VLP) vaccine. [Abstract] *International Society for Infectious Diseases.* 2006 June 15–18; Lisbon