J Interdiscipl Histopathol 2013; 1(4): 212-216 *ISSN: 2146-8362*

Review Article

Role of HPV Vaccine in the Prevention of Cervical Cancer

Saleh JA [1], Yusuph H[2], Zailani SB[3], Aji BM[4]

[1]*Hospital Services Management Board, Yola, Adamawa State, Niegeria*
[2]*Department of Medicine, University of Maiduguri Teaching Hospital, Maiduguri, Borno State, Nigeria*
[3]*Department of Microbiology, University of Maiduguri Teaching Hospital, Maiduguri, Borno State, Nigeria*
[4] *Department of Medicine, Hull Royal Infirmary, UK*

Received: January 08, 2013

Accepted: January 19, 2013

Published Online: January 28, 2013

DOI: 10.5455/jihp.20130119122700

Corresponding Author:
Dr Jalal-Eddeen Abubakar Saleh,
Hospital Services Management Board,
Yola, Adamawa State, Nigeria
drjalals@yahoo.com

Keywords: Cervical Cancer, Human Papilloma Virus, Pap Smear, Vaccination

Abstract

Objective: Cervical cancer which affects relatively young women of child bearing age is considered to be the second most common cancer in women and a leading cause of cancer-related deaths in developing countries, a reflection of global health inequity. There are more than 450,000 newly diagnosed cases annually with over a quarter of million deaths recorded out of which over 80 percent are from the developing countries especially Africa, South Asia, South and Central America, and the Caribbean, with an exponential rise expected from this figure by 2020. The preventive measures available (Pap smear and HPV vaccine) aimed at reducing morbidity and mortality associated with this disease, has been shown to be very effective but difficult to implement especially in the developing countries partly due to lack of resources and mainly lack of government commitment amongst other things. This forms the basis of this review to look at the position of HPV vaccine in the prevention of cancer of the cervix.

Methods: In the course of this write-up, relevant literatures were reviewed using manual library search, relevant websites and internet articles. The key words employed were: cervical cancer, human papilloma virus, pap smear and vaccination.

Results: It has been shown that, where resources permits, combining HPV vaccine in combination with pap smear screening methods especially to high risk group would greatly reduce the morbidity and mortality associated with cancer of the cervix.

Conclusions: Although there are so many essential questions still unanswered, considering the havoc caused by this preventable gynaecological malignancy and coupled with the ever increasing costs of its treatment, the advantages of using HPV vaccine in addition to routine Pap smear as a means of preventing cancer of the cervix greatly outweighs the disadvantages. However, there is the need for caution to be adhered to when it comes to large scale vaccination programs in view of the fact that sufficient evidence is still lacking on the safety of the vaccines in the long-term.

INTRODUCTION

Infection with oncogenic types of Human Papilloma Virus (HPV) is the cause of cervical cancer (100%), anal cancers (90%), vulvovaginal cancers (40%), oropharyngeal cancers (at least 12%) and oral cancers (3%). Of all the different types of the HPV, types 16 and 18 causes about 70% of cervical cancers [1,2].

Cancer of the cervix affects relatively young women in their reproductive age, thus an increase burden on the family in terms of their well being, absence from work, domestic activities, school attendance of their wards and nutritional status of the family on a larger scale [3].

Several literatures have shown cervical cancer to be the second most common cancer in women across the globe, a reflection of global health inequity, with more than 450,000 newly diagnosed cases each year. Of these number, over a quarter of million deaths are recorded yearly out of which over 80 percentage are

from the developing countries especially Africa, South Asia, South and Central America, and the Caribbean, with an exponential rise expected from this figure by 2020 [3, 4]. The reasons for this higher percentage of deaths seen in the low income countries are multifaceted and include lack of screening methods, inadequacies of the Pap smear, poor health infrastructure, lack of government commitment and the ever increasing health inequalities between the developed and developing countries.

In Nigeria, although there is some increase level of awareness in Pap smear [5] though not necessarily practicing it, the issue of HPV vaccine is entirely something new for reasons which are not unconnected to the ones mentioned above.

It has been documented that even in the world most industrialised countries, the disease burden on their health systems are enormous with a gloomy in the developing countries of especially sub-Saharan Africa. In a study[4] carried out by Lowndes, she observed that ''in Western Europe, about 33,500 new cases of cervical cancer are diagnosed each year and 15,000 women die from the disease. In the United States, an estimated 13,000 new cases, and 4000 deaths, occurred in 2003''. The study further observed that ''the incidence of cervical cancer increases with age, rising sharply to 15 cases per 100,000 between the ages of 20 and 35 years, then fluctuating around 15-20 cases per 100,000 in older women''. In addition and to further support the need for adopting preventive measures the study noted that ''the costs of treatment are high and rising: in the United States in 1994, it was estimated that the combined costs of treating cervical cancer exceeded $4.5 billion, more than any other single sexually transmitted infection (STI) with the exception of HIV''.

Cancer of the cervix could either be squamous cell type (at least 75%, which can be invasive or non-invasive) or adenocarcinoma (about 15%, which is increasingly becoming common in younger women within the last few decades). The squamous type could further be sub-divided into cervical intra-epithelial neoplasia (CIN) and carcinoma in-situ (CIS); these two represent the earliest stages associated with the development of invasive cervical cancer (ICC). There is now strong and convincing evidence that there is strong association between sexual exposure, Human papilloma virus (HPV) and development of CIS and CIN. The HPV has several types and about 20-30% of infected women harbour more than one HPV type. The types of HPV include 6,11,16,18,31,33,45 etc. in addition to some unclassified types. It is a simple virus with a small and stable genome, not prone to mutation thus making it suitable for vaccine development. HPV vaccines which could be monovalent, bivalent, quadrivalent or multivalent [4] have proven to be promising at least in the short term in the prevention of cancer of the cervix [3, 4].

In a retrospective study conducted by Mayun et al [6] in Maiduguri, north-eastern part of Nigeria, of diagnosed registered cases of cancer of the cervix, he noted that cervical cancer is still the most common gynaecological malignancy in developing countries despite being largely preventable. He observed in between 1989 to 2004, a total number of 491 cases were diagnosed and out of this figure, 432 (88.0%) were squamous cell carcinoma and 59 (12%) were non-squamous cell type. Of the 59 non-squamous type, 42(71.2%) were endocervical adenocarcinomas a clear indication that adencarcinoma is the commonest in the non-squamous type. Other types include serous papillary, clear cell, and adenosquamous carcinomas each at 2(3.4%) and the remaining 7(11.9%) cases were metastatic choriocarcinomas. In related but different retrospective study by Ijaiya et al in Ilorin, south west Nigeria, cancer of the cervix accounted for 63.1% of histologically confirmed gynaecological cancers [7].

Olatunji et al suggested a number of measures aimed at reducing the incidence and morbidity of cancer of the cervix in Nigeria; these measures include: mass health education on the importance of reporting symptoms early and regular Pap smear screening of especially those at risk [8].

In clinical practice, there are several measures aimed at controlling cervical cancer which in addition to the traditional Pap smear, are high-tech procedures like the DNA hybrid capture, nucleic acid amplification technology and HPV vaccination [3, 4].

HPV VACCINE: Historically, vaccines were not developed overnight as it takes enormous time, energy, patience and resources to be able to achieve that. It is an ongoing process which dated back to over two centuries ago when Edward Jenner first developed a small pox vaccine. However, there are several other vaccines which were developed by renowned figures in medical history whose contributions tremendously help in the control and spread of life threatening diseases; most of these vaccines were developed empirically and from either killed or attenuated whole organism.

It was in 2006 that HPV vaccines were licensed in the USA for use in females aged 9 to 26 years of age with the aim of preventing cancer of the cervix, precancerous genital lesions and genital warts. It was indeed an important milestone as in the short term the vaccine was able to reduce the incidence of precancerous cervical lesions caused by HPV16 and HPV-18 strains and prevent infections with HPV-16 and HPV-18 strains especially in those who have not previously been infected with these strains [9-14].

It is worthy to note that the real impact of the HPV vaccine on cancer of the cervix would not be observable until after at least a decade [15]. The outstanding results so far noted with the use of the HPV vaccine are not without some hiccups as there are still some un-answered questions especially the safety and long term side effects of the vaccine; these and some other issues limits the wide spread acceptance of the vaccine a situation often seen in female subjects and some parents who say that their daughters are not sexually active and thus not at risk.

Although the HPV vaccine aims to significantly reduce HPV infection rate at the population level in addition to preventing cervical cancer, there is still room for Pap smear and other cytological screening to help in detecting cellular changes (pre-cancerous and cancerous) which often results from HPV infection.

Studies have shown HPV infection to be the most common sexually transmitted disease in young people with an estimated figure of 4.6 million new cases recorded in the USA in 2000. Male individuals play an important role in the spread of this infection to their sexual partners; this has led to some trials of the HPV vaccine in male subjects to be able to promote its use among them [16]. The advantages and disadvantages of the HPV vaccine could be summarised as follows [4, 15]:

ADVANTAGES:

- High efficacy of the vaccine in preventing transient HPV infection, persistent HPV infection and pre-invasive disease, as evidenced by according-to-protocol (ATP) analyses with their respective percentages as 91.7%, 100% and 100% at 18 months. This high efficacy is seen in both HPV 16 and 18 types; this is especially important in the sense that HPV 18, which is closely associated with cervical adenocarcinoma and difficult to detect by Pap smear screening.
- The issue of sensitivity of Pap smear for the detection of precursors of ICC is sub-optimal and variable ranging from 30-90% and the specificity is in the range of 85-100% but its predictive value for accurately predicting the risk of development of CIS and ICC is imperfect; thus vaccination would greatly reduce the issue of low sensitivity associated with Pap smear and other methods.
- HPV vaccination helps do away with the issue of carrying out multiple screening tests with a view to having higher sensitivities. These multiple tests are often complex, costly and have low specificities.
- The seroconversion rate reported was 99.7% and mean antibody titre were about 60-fold higher in vaccinated than the unvaccinated naturally HPV 16 infected women.
- In the case of vaccination, there would not be a need for laboratory and or high human expertise as in the case of other screening methods. The man power required to carry out the vaccination would not be as much as that of the screening exercise where in addition they should be highly skilled to ensure good results.
- The logistics involved would not be much as is the case with mass screening; this is more so especially in most developing countries of Africa, South Asia, South and Central America, and the Caribbean, where the goal of adequate coverage of the population is practically impossible.
- Effective multivalent vaccine, consisting of all the possible HPV serotypes (when developed) would greatly reduce the frequency of abnormal Pap smears and pre-invasive disease and thus the costs of follow-up.
- It can complement screening programmes especially in women who do not regularly go for screening, thus a cost effective approach on the long-term.
- It could reduce the prevalence as well as the squeal of HPV 16 and 18 infections thus making HPV screening to replace cervical cytology thus a reduction in cost to the health care systems and further improving the performance of screening programmes.
- If both males and females are vaccinated, it would lead to herd immunity among the population and further interrupt transmission of the HPV with a resultant reduction in prevalence at the population level.
- The vaccine has the advantage of being both preventive and also the potential of stimulating immunity in those women who are already infected with the HPV.
- In view of the stress involved with Pap smear screening to the patient, compliance is likely to be high with vaccination.

DISADVANTAGES:

- The technology involved couple with high cost of HPV vaccine production.
- Logistics involved in recruiting and educating staff for the exercise, and running the HPV vaccination program would strain the meagre resources allocated to the health sector.

- The vaccine is only meant for women and not men who play an important role in the transmission of the infection.
- Therapeutic vaccines aimed at eradicating or reducing HPV-infected cells, although promising, are lacking at this stage.
- The HPV vaccine protects against HPV-16 and HPV-18 strains thus putting pressure to the other strains which could lead to emergence of other significant strains.
- These vaccines currently in use, and even the ones under evaluation, don't protect against all forms of cervical oncogenic hence the need to continue with Pap smear screening. This further creates additional burden to the health sector further jeopardising the aim of the program.
- The need to develop multivalent vaccine (comprising all the types of HPV) to confer immunity against all types.
- The duration of the antibody response after the HPV vaccination to be able determine when booster shots are to be given remains to be determined thus undermining the objective of the vaccine.
- Vaccinated women may feel they are at low risk and may decide to stay away from the recommended screening thus reversing the gains of the vaccination; this may on the long run lead to increase in cases of cancer of the cervix.
- The need to employ additional manpower to enlighten the public on importance of the vaccine so as to remove any negative belief on the vaccine; this would attract some additional administrative and logistical expenses to an already poorly funded health with a resultant failure at the end.
- Considering the fact that the vaccine is foreign to the human system, some individuals are prone to have some adverse reaction to it which could be life threatening.
- Those vaccinated could indulge themselves into promiscuous acts believing that they are immune to the HPV thus predisposing them to other forms of sexually transmitted diseases.
- The overall effect of the vaccine against cervical cancer remains unknown as the real benefit cannot be judged until after a decade or more.
- The issue of vaccination destroying natural immunity since most HPV infections are often cleared by the immune system.
- In the event of vaccine failure, recipients would not be fully protected from HPV virus or other forms of oncogenic viruses associated with cervical cancer thus exposing them high chance of getting infected form other strains of the HPV virus.
- The vaccine was effective in the prevention of precancerous cervical lesions caused by HPV 16 and 18 but not cervical cancer thus the need of cost benefit analysis before adopting the use of the vaccine.

CONCLUSION:

This review was able to underscore the importance of using HPV vaccine as an important means of preventing cancer of the cervix. The vaccine is also aimed at reducing HPV infection rate at the population level with a view to lower the incidence of cervical cancer. It further underscored the importance of adopting routine Pap smear to be able to detect cellular changes (pre-cancerous and cancerous) that often results from HPV infection. Furthermore, as with most health programmes which are capital intensive and especially in resource poor settings, there is a need for conducting cost-benefit analysis to be able to know which group of people would benefit from the vaccine.

In line with principles of vaccines use, there is the need to know baseline rates of incidence and prevalence of cervical cancer as well as age distribution in any given population as a preliminary measure prior embarking on the vaccination. Furthermore, the need for post-implementation surveillance should not be overlooked and this is by monitoring changes in incidence of cervical cancer, mortality, morbidity, hospitalizations (surgeries for cervical cancer), change in circulating of HPV types, uptake of vaccine, vaccine side-effects and vaccine failures [17].

REFERENCES:

1. Clifford G, Franceschi S, Diaz M, Muñoz N, Villa LL. Chapter 3: HPV type-distribution in women with and without cervical neoplastic diseases. Vaccine 2006; 24: Suppl 3:S26-S34.
2. Clifford GM, Smith JS, Plummer M, Muñoz N, Franceschi S. Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. Br J Cancer 2003; 88:63-73.
3. Agosti JM, Goldie SJ. Introducing HPV vaccine in developing countries-Key challenges and issues. N Engl J Med 2007; 356;19:1908-1910.
4. Lowndes CM. Vaccines for cervical cancer [Editorial Review]. Epidemiol. Infect 2006; 134: 1-12.
5. Dim CC, Ekwe E, Madubuko T, Dim NR, Ezegwui HU.

Improved awareness of Pap smear may not affect its use in Nigeria: a case study of female medical practitioners in Enugu, southeastern Nigeria. Trans R Soc Trop Med Hyg. 2009;103(8):852-854.

6. Mayun AA, Nggada HA, Audu BM Pindiga UH, Khalil MI, Musa AB. Histopathological analysis of non-squamous cell malignancies of the uterine cervix in Maiduguri, Nigeria. Afr J Med Sci 2008;37(4); 369-373.
7. Ijaiya MA, Aboyeji PA, Buhari MO. Cancer of the cervix in Ilorin, Nigeria. West Afr J Med 2004;23(4); 319-322.
8. Olatunji AO, Sule-Odu AO. Cancer of the cervix. Niger Postgrad Med J 2005;12(4):308-311.
9. The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915-1927.
10. Ault KA. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. Lancet 2007;369: 1861-1868.
11. Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, Tang GW, Ferris DG, Steben M, Bryan J, Taddeo FJ, Railkar R, Esser MT, Sings HL, Nelson M, Boslego J, Sattler C, Barr E, Koutsky LA; Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I Investigators. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007; 356:1928-1943.
12. Paavonen J, Jenkins D, Bosch FX, Naud P, Salmerón J, Wheeler CM, Chow SN, Apter DL, Kitchener HC, Castellsague X, de Carvalho NS, Skinner SR, Harper DM, Hedrick JA, Jaisamrarn U, Limson GA, Dionne M, Quint W, Spiessens B, Peeters P, Struyf F, Wieting SL, Lehtinen MO, Dubin G; HPV PATRICIA study group. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. Lancet 2007; 369:2161-2170. [Erratum, Lancet 2007; 370: 1414].
13. Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins CM, Jenkins D, Schuind A, Costa Clemens SA, Dubin G; HPV Vaccine Study group. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. Lancet 2006; 367:1247-1255.
14. Lacey CJ, Lowndes CM, Shah KV. Chapter 4: burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease. Vaccine 2006; 24 (Suppl 3):S35-S41.
15. Charlotte JH. Human papilloma virus vaccination-reasons for caution. N Engl J Med 2008; 359:861-862.
16. Weinstock H, Berman S, Cates W Jr. Sexually transmitted disease among American youth: incidence and prevalence estimates, 2000. Perspect Sex Reprod Health 2004; 36:6-10.
17. Noah N. Controlling Communicable Disease, Open University Press, London 2006.