CERVICAL CANCER VACCINATION, A STEP TOWARDS PREVENTION : A REVIEW

Shahanara Chowdhury[1] Afroza Ferdous[2]

Summary

Cervical cancer is the second most common cancer among women in the world. The human papilloma virus (HPV) was conclusively identified as the etiological factor for anogenital malignancy, including inducing cervical cancer. Investigations during the last two decades have been concentrating on producing a vaccine against HPV virus. Thus prevention of HPV infection has been the main purpose and vaccination is expected to reduce up to 70% of related cervical cancer and prevent precancerous and cancerous lesions of the genitalia. However, screening programs are still essential for those who have already been exposed to the high risk forms of the virus. Educational and information programs continue to play important roles to increase the success rate of screening. Two vaccines are now available for primary prevention. They generate neutralizing antibodies to HPV capsid protein. The vaccines have been shown to confer nearly 100 per cent protection against cervical pre-cancers and genital warts caused by HPV types 16/18 in HPV naive population with few or no side effects. Though there is some cross-protection, around 30 per cent of cervical cancers will not be prevented by the vaccine. Vaccination and screening, which are complementary and synergistic, now constitute the new paradigm for prevention of this disease.

Key words

Cervical cancer; HPV vaccine; prevention.

Introduction

Globally, cervical cancer is one of most common cancers in women, killing about 0.25 million women per year, commonly in 30–50-year-old women. More than 80 % of cervical cercer occur in developing countries where neither population-based screening nor optimal treatment is available than developed countries [1]. In developed countries, incidence and mortality rates for cervical cancer have declined dramatically, due to the effectiveness of screening programs that assess cervical cytology by Papanicolau smear [2,3].

1. Professor of Obstetrics & Gynecology
Chittagong Medical College, Chittagong
2. Junior Consultant of Obstetrics & Gynecology
Chittagong Medical College, Chittagong

Correspondence : Dr Shahanara Chowdhury
email : shahanacmc@yahoo.com

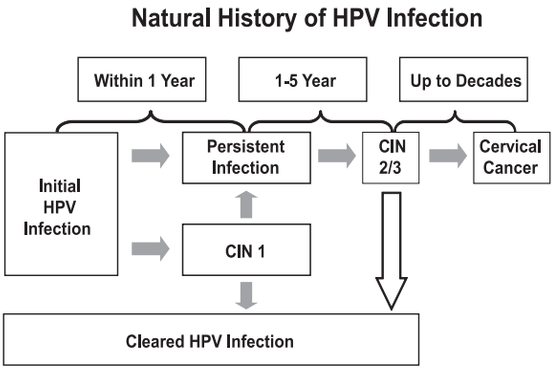
Cervical cancer is still a largely preventable disease, with a known causative agent in 95% of cases by human papilloma virus (HPV). The other 5% of cervical cancer cases may be unrelated to HPV infection [3-6]. Bangladesh is a country, who shares a high prevalence of cervical cancer. The Government has taken a coordinated program of population based cervical cancer screening program with UNICEF which is monitoring from Bangabandhu Sheikh Mujib Medical University (BSMMU) (Colposcopy unit). The most cost effective and easily performed screening options like visual inspection after acetic acid application (VIA) test and their subsequent follow up as per protocol is implementing phase wise. Those having positive finding is referred for further screening with colposcopy. The aim of colposcopy is by single visit approach, screening and treatment (see & treat) of cervical diseases. Two vaccines are now available for primary prevention. They generate neutralizing antibodies to HPV capsid protein. The vaccines have been shown to confer nearly 100 per cent protection against cervical pre-cancers and genital warts caused by HPV types 16/18 in HPV naive population with few or no side effects. Though there is some cross-protection, around 30 per cent of cervical cancers will not be prevented by the vaccine. Vaccination and screening, which are complementary and synergistic, now constitute the new paradigm for prevention of this disease [7-10].

HPV in natural history of cervical carcinogenesis

HPV is the most common sexually transmitted infection (STI) and the women acquiring this infection when they initiate their sexual life. The peak incidence of this infection contacted between 20 and 25 years and then come down abruptly after the age of 30 years as most of the infected women acquire the natural immunity against the infection and clears it. Estimated 90 percent of the immune-competent women have been found to clear the HPV 16 infection within 5 years without any treatment [11,12]. Women who cannot clear the infection and have persistently infected cervix are at the highest risk of developing cervical cancer [13,14].

The HPV virus infects the basal keratinocytes through metaplastic epithelium present in the transformation zone of squamo-columner junction of the cervical epithelium. Persistent infection of cervix with HPV, the viral genome gets integrated to the host genome that over-expresses two onco-proteins,

E6 and E7. The E6 proteins degrade p53 genes resulting in genetic instability and accumulation of mutated deoxyribonucleic acid (DNA) that trigger uncontrolled cellular multiplication [15,16]. The E7 protein degrades the active form of retinoblastoma protein leading to the progression of the cell into the S-phase of the cell cycle with subsequent unregulated cell replication. Thus unregulated cellular proliferation in the affected epithelium leads to development of cervical neoplasia [15-17].



Cervical cancer is preceded by HPV induced premalignant condition known as cervical intraepithelial neoplasia (CIN), graded from CIN 1 to CIN 3 depending on the severity. While majority of CIN 1 lesions are self-limiting, CIN 2 and CIN 3 are considered true pre-malignant lesions. Given adequate follow up time, specially the CIN3 lesions, 30 percent to 50 percent of them will progress to invasive cancers. Cervical cancer screening detects the disease at the CIN 2/3 stage when appropriate interventions prevent further progression to invasive cervical cancer (ICC). The vaccines prevent even the development of CIN 2/3 by preventing persistent infection of certain high risk HPVs, thus eliminating the chance of development of invasive cancer in the future by those HPV types [18,19].

Human papilloma vaccines

1. Bivalent vaccine (Cervarix™, GlaxoSmithKline Biologicals)
2. Quadrivalent vaccine (Gardasil™, Merck) [8]

Mechanism of action of the HPV vaccines

The bivalent vaccine is used to protect against high-risk HPV types 16 and 18 and a quadrivalent vaccine is designed to protect against HPV 16 , 18 and HPV 6 , 11 (low-risk causing genital wart). These vaccines aim to prevent infection from HPV types 16 and 18, since these two types are most carcinogenic and are responsible for majority of cervical cancers. The two available HPV vaccines both contain virus-like particles (VLPs), derived from the L1 surface protein of the respective types of the virus. These vaccines are made using recombinant vaccine technology; they are not live vaccines. HPV vaccines are prophylactic, that is, designed to prevent initial HPV infection. They are not therapeutic vaccines and will not clear an existing HPV infection.

The VLPs are non-pathogenic and cannot infect cells, since they do not have viral genome. The vaccines induce high titer of serum immunoglobulin G antibody against respective HPV types, which is secreted in the cervico-vaginal secretion and is also exuded from the micro-abrasions in the epithelium. Presence of the antibodies at the point of viral entry ensures the neutralization of the virus before it gets an opportunity to bind to infect the basal keratinocytes [17,18]. However, there is no routine diagnostic serological assay for detecting HPV antibodies. No protective antibody threshold has been established, and serologic testing before or after vaccination is not required [20-22].

Following questions need to be addressed before providing vaccination service :

Who should be vaccinated ?

The vaccines should be administered to girls and young adults before they become sexually active [5,6,8].

Should be HPV Vaccination Performed on Men too?

Since HPV infection is one of sexually transmitted diseases which can be transmitted by both women and men, vaccination is therefore recommended for both sexes. However, the efficacy of HPV vaccine on men is still unclear and needs more evaluation [8].

When vaccine should be given ?

1. Cervarix : For females 9-26years ,not approved for males or for the prevention of genital warts .
2. Gardasil: For females 9-26years ,for males 9-26 years for the prevention of genital warts [23,24].

Administration of vaccines

The dose of Gardasil and Cervarix is 0.5 mL administered intramuscularly. The recommended schedule for Gardasil is 3 doses administered at intervals of 0, 2 and 6 months. The recommended schedule for Cervarix is 3 doses administered at intervals of 0, 1 and 6 months [23,24].

Safety of vaccine

HPV vaccines are approved for use in over 100 countries, with more than 100 million doses distributed worldwide. Extensive clinical trial and post-marketing safety surveillance data indicate that both Gardasil and Cervarix are well tolerated and safe.

The main side effect of the vaccines is local reactions at the injection site (pain, redness and swelling) which occur in about 80% of vaccine recipients. Meta-analyses on pooled data from multiple clinical trials on both HPV vaccines have shown no increase in the risk of serious adverse events among vaccine recipients compared with control/placebo recipients No deaths reported in safety surveillance systems.

The Post-marketing surveillance data have indicated that anaphylaxis can occur rarely following administration of Gardasil . If a hypersensitivity reaction (such as generalised urticaria or angioedema) is reported to have occurred in close temporal association (usually hours or a few days) with a previous vaccine dose, careful clinical review and possibly re-vaccination under close clinical supervision is indicated [23,24].

Contraindications / Precautions

HPV vaccine should not be given to anyone who has experienced an anaphylactic reaction to any component of the vaccine (including yeast for Gardasil) or following a previous dose of vaccine.

HPV vaccine should not be administered during pregnancy. If vaccination is inadvertently administered during pregnancy, the rest of the vaccination course should be deferred until after pregnancy. Females who inadvertently receive a dose of HPV vaccine around the time of conception or during pregnancy should be informed that the scientific evidence suggests there is no harm to the pregnant woman or her fetus if vaccination has occurred inadvertently during pregnancy. As recommended for all vaccines, HPV vaccine should not be given during any moderate to severe febrile illness [22-25].

Cost effectiveness of HPV vaccines

Cost of the HPV vaccines and its availability is a great concern for the policy makers, service providers and also for the consumers .For this reason it is not included in the national immunization program. Till date the only vaccine available in our country is bivallent Cervarix . The estimated price for this HPV vaccine is 1650 taka per dose . It is much more expensive than the other regular EPI vaccines.

Conclusion

Formulation of a National guidelines for cervical cancer control program and their implementation should be a national priority. The main impedance for the implementation of such program are attitudes of the service providers, quick access to the screening service, vision of the socio-medical organization, political commitment, public awareness, availability of fund and cost of the vaccine. Effective screening program and in combination with awareness campaign, monitoring system with vaccination for HPV infection and its inclusion in the national EPI and other preventive services should be the challenge for both the Government of Bangladesh and the Obstetrical and Gynaecological Society of Bangladesh (OGSB). OGSB in collaboration with other stakeholders has a great role to play to convince the policy makers and health administrations to be sensitized to give this a national priority program using available service infrastructure delivery models as suitable to them. The HPV vaccine is a safe and effective option for cervical cancer prevention.

Disclosure

All the authors declared no competing interest.

References

1. Partha Basu & Debjani Chowdhury .Cervical cancer screening & HPV vaccination:A comprehensive approach to cervical cancer control. Indian J Med Res 2009;130:241-246.

2. Human papillomavirus (HPV) vaccines for Australians | NCIRS Fact sheet: March 2013.

3. Ian H. Frazer. prevention of cervical cancer through papillomavirus vaccination january 2004 | volume.

4. Canadian Cancer Society's Steering Committee. Canadian Cancer Statistics 2010. Toronto: Canadian Cancer Society;2010.

5. Canadian Cancer Society's Steering Committee. Canadian Cancer Statistics 2009. Toronto: Canadian Cancer Society;2009.

6. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol. 2006; 24(14):2137-2150.

7. Miller AB, Chamberlain J, Day NE, Hakama M, Prorok PC. Report on a Workshop of the UICC Project on Evaluation of Screening for Cancer. Int J Cancer. Nov 15 1990;46(5):761-769.

8. Mandic & T. Vujkov Human papillomavirus vaccine as a new way of preventing cervical cancer: a dream or the future? Annals of Oncology 2004;15:197-200.

9. Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics, 2001. CA Cancer J Clin 2001; 50: 7–33.

10. Boffetta P, Parkin DM. Cancer in developing countries. CA Cancer J Clin 1994; 44: 81–90.

11. Lorincz AT, Lancaster WD, Kumman RJ et al. Characterization of human papillomaviruses in cervical neoplasia and their detection in routine clinical screening. In Petro R, zur Hausen H (eds): Viral Etiology of Cervical Cancer. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press 1986; 225.

12. Stanimirovi B. National program of early detection and treatment of uterine cervical cancer [in Serbian]. Archiv Oncol 2000; 8: 61–64.

13. zur Hausen H. Human papillomaviruses in the pathogenesis of anogenital cancer. Virology 1991; 184: 9–13.

14. Coggin JR, Zur Hausen H. Workshop on papillomaviruses and cancer. Cancer Res 1979; 39: 545–546.

15. Richart RM. Cervical intraepithelial neoplasia. Pathol Annu 1973; 8:301–328.

16. National Cancer Institute Workshop. The 1988 Bethesda System for reporting cervical/vaginal cytological diagnoses. J Am Med Assoc 1989; 262: 931–934.

17. Lucija Tomljenovic, Judy Wilyman , Eva Vanamee , Toni Bark , Christopher A. HPV vaccines and cancer prevention, science versus activism . Tomljenovic et al. Infectious Agents and Cancer 2013, 8:6 http//www. infectgentscancer.com/ cont/8/1/6 .

18. Mojgan Karimi Zarchi1, Nadereh Behtash, Zohreh Chiti1, Saeed Kargar . Cervical Cancer and HPV Vaccines in Developing Countries. Asian Pacific J Cancer Prev, 10, 969-974 .

19. American College of Obstetricians and Gynecologists . ACOG practice Bulletin 2003. 45: Cervical Cytology Screening. Obstet Gynecol, 102, 417-27.

20. Announcement the Society of Gynecologic Oncologists Statement on a Cervix Cancer Vaccine 2006. Gynecol Oncol, 101, 377.

21. Behbakht K, Lynch A, Teal S, et al). Social and cultural barriers to apanicolaou test screening in an urban population 2004 .Obstet Gynecol, 104, 1355-61.

22. Judy Wilyman MSc. The pathogenesis of Human Papillomavirus (HPV) in the development of cervical cancer: are HPV vaccines a safe and effective management strategy? BSEM March 2011.The health hazard of diseases prevention .

23. National Health Policy 2002. Ministry of Health & Family Welfare. Government of India. New Delhi. Available from: http:// mohfw.nic.in/np2002.htm, 2009;4.

24. Sankaranarayanan R, Thara S, Sharma A, Roy C, Shastri S, Mahé C et al. Multicentre Study Group on Cervical Cancer Early Detection in India. Accuracy of conventional cytology: results from a multicentre screening study in India. J Med Screen 2004; 11 : 77-84.

25. Dabash R, Vajpayee J, Jacob M, Dzuba I, Lal N, Bradley I et al . A Strategic Assessment of Cervical Cancer Prevention and Treatment Services in 3 Districts of Uttar Pradesh, India. Reprod Health 2005, 2 : 11-18.