Human Papilloma Virus Vaccine for Cervical Cancer Prevention

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Abstract:

HPV infection is estimated to be responsible for about 5% of human cancers worldwide. Among all HPV-associated malignancies, cervical cancer is the most important cause of morbidity and mortality worldwide. Cervical cancer is the fourth most common cancer in women worldwide and leading cause of cancer death among females in less developed countries. Persistent HPV infection is a necessary cause of invasive cervical cancer with a prevalence of 99.7% in cervical cancer worldwide.At least 70% of cervical cancers are caused by HPV 16 and HPV 18. HPV vaccination in combination with regular screening offers the most effective way for women to be protected against cervical cancer.The global burden of cervical cancer falls heaviest on the developing countries which haven't introduced the HPV vaccine as part of their national public health strategy to prevent and control cervical cancer. Different studies showed a drop in the prevalence of HPV associated diseases in vaccinated populations. Sustained efficacy, immunogenicity, and safety of the bHPV vaccine were observed in the final analysis of a follow-up study up to 9.4 years postvaccination. Cervical cancer is a major public health problem in Bangladesh. There has been little success with screening program against cervical cancer in Bangladesh. Therefore, a National HPV Vaccination Program seems to be the window of opportunity to reduce the mortality and morbidity of cervical cancer in Bangladesh.

Keywords: Cervical cancer, Human Papilloma Virus (HPV), HPV vaccine.

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Introduction:

Cervical cancer is a major public health problem worldwide. It is the 4th most frequently diagnosed cancer in women worldwide, with an estimated 570,000 new cases in 2018. It is also the 4th leading cause of cancer death, with an estimated 311,000 deaths in 2018. Cervical cancer is the 2nd most commonly diagnosed cancer and leading cause of cancer death among females in less developed countries.[1] Cervical cancer is the 2nd leading cause of female cancer in incidence and 3rd leading cause of female cancer deaths among Bangladeshi women with an estimated 8,068 new cases and 5,214 deaths in 2018.[2]

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Human papillomavirus (HPV) is the virtually necessary cause of carcinoma cervix. HPVs causing not only the vast majority of cervical (99.7%), but also a substantial proportion of other anogenital and head and neck cancers.[3,4] Among all HPV-associated malignancies, cervical cancer is the most important cause of morbidity and mortality worldwide. Approximately 70% of cervical cancers worldwide are associated with two high-risk HPV types (16/18), while other high-risk HPV types 31, 33, 35, 45, 52 and 58 are responsible for approximately 20% case.[5,6] HPV type 16/18 infection was detected in 40.42% of the women in Bangladesh with cervical epithelial cell abnormality.[7] HPV type 16 was detected in 81.82%, type 18 in 9.09% and type 45 in 6.06% cases of cervical carcinoma in Bangladesh.[8]

In developed countries, incidence and mortality of cervical cancer has been lowered by effective population-based screening program with Pap smear and or HPV DNA testing.[9] Government of Bangladesh with the support of UNFPA has taken initiative to develop a cervical cancer screening

program by visual inspection with acetic acid (VIA), which was considered to be a feasible method for screening cervical cancer in the present socio-economic context. It has been estimated that only 5% of the women in developing countries have been screened for cervical dysplasia compared with about 40% to 50% of women in developed countries.[10]

One of the greatest medical breakthroughs in the last century is the development of HPV vaccine against cervical cancer by Professor Frazer and Dr Jian Zhou.[11] HPV related anogenital cancers can be prevented using a prophylactic vaccine. The two prophylactic HPV vaccines, quadrivalent HPV type 6/11/16/18 vaccine and bivalent HPV type 16/18 vaccine, were licensed in 2006 and 2007 under the names of Gardasil® and Cervarix® respectively.[12] Recently nine-valent HPV type 6/11/16/18/31/33/45/52/58 vaccine with broader cancer coverage has also received the United States Food and Drug Administration (US-FDA) approval in October 2016 under the name of Gardasil9®.[13] Different studies in USA, Australia and Scotland have begun to show a drop in the prevalence of HPV associated diseases both in vaccinated and non-vaccinated populations indicating establishment, of herd immunity and also provide cross- protection.[14-17] Khatun S et al[18] observed high immunogenicity and safety of the bHPV vaccine among Bangladeshi adolescent girls at 7 months of vaccination.Sustained efficacy, immunogenicity, and safety of the bHPV vaccine were observed in the final analysis of a follow-up study up to 9.4 years postvaccination.[19]

HPV vaccine has introduced in Bangladesh by the Ministry of Health and Family Planning (MoHFP), with support from the Global Alliance for Vaccines and Immunizations (GAVI) for two years in Gazipur district and if it is successful, GAVI will provide support for national introduction of HPV vaccine.[20] There has been little success with screening program against cervical cancer, which is a major public health problem in Bangladesh. Therefore, a National HPV Vaccination Program will reduce the mortality and morbidity of cervical cancer in Bangladesh.The objective of the review article is to evaluate the current status of the cervical cancer prevention achieved by HPV vaccination worldwide.

Rationale of the review

National HPV vaccination programs have been implemented in many countries to prevent cervical cancer. But no National HPV Vaccination Programhas yet been started in Bangladesh and also no review has been done related to HPV Vaccination so far. Hence, this review has been conducted to explore different aspects of HPV vaccines in depth which will help to recommend a National HPVvaccination Program for prevention of cervical cancer among Bangladeshi women by a low-cost bHPV vaccine.

Review of literature

Human papillomavirus (HPV) vaccine for preventing HPV induced malignancy is a widely studied topic for physicians. Different authors explained different aspects of HPV, its malignant potential, its preventive measures through vaccination and HPV vaccines immunogenicity, efficacy, safety etc through their own view. Articles related to Human papillomavirus (HPV) vaccine were retrieved from different journals, web pages and books. From them 40 papers were included to prepare this manuscript.

Role of HPV in cancers:

The connection between persistent infection with HPV and cervical cancer was first described by Harald Zur Hausen in 1977. In 1983 & 1984 Zur Hausen and his collaborators identified role of HPV 16 & 18 in cervical cancer and in the course of the next 12 years of research it has been recognized as a carcinogen influencing its development.[21] This finding laid the ground for the idea of a vaccine against HPV infection and cervical cancer, and in 1999 it finally became clear that persistent HPV infection is a necessary cause of invasive cervical cancer.[3] HPV infection is commonly found in the anogenital tract of men and women with and without clinical lesions. The etiological role of HPV infection among women with cervical cancer is well-established, and there is growing evidence of its central role in other anogenital cancers (anus, vulva, vagina, penis), head and neck cancers. HPV is also responsible for diseases e.g recurrent juvenile respiratory papillomatosis and genital warts, both mainly caused by HPV 6/11.[22]

Structure[23] and gene functions[24] of HPV:

HPV is a relatively small non-enveloped double-stranded DNA virus in the family Papillomaviridae. It is associated with histone-like proteins and protected by a capsid formed by two late proteins, L1 and L2. Each virion contains 72 copies of the L1, the major component of the capsid, and a variable number of copies of L2, a secondary component of

the viral capsid. DNA containing approximately 8000 base pairs and harboring an average of 8 open reading frames (ORFs). In a functional point of view, the HPV genome is divided into three regions. The first is a long control region (LCR) that has regulatory function of the transcription of the E6 and E7 viral genes. The second is an early region (E), consisting of six ORFs: E1, E2, E4, E5, E6, and E7, which encodes no structural proteins involved in viral replication and oncogenesis. The third is a late (L) region that encodes the L1 and L2 structural proteins.

Table1 different human papillomavirus gene functions[24]

Gene Category	Gene	Function
Early genes	E1	Viral replication
	E2	Modulation of transcription and replication
	E3	Unknown
	E4	Productive viral infections
	E5	Transforming properties
	E6	Oncoprotein; interaction with p53 protein
	E7	Oncoprotein; interaction with pRb protein
	E8	Unknown
Late genes	L1	Major capsid protein
	L2	Major capsid protein

Life cycle of HPV[25]:

The viral life cycle refers mainly to high-risk mucosotropic HPVs and is commonly extrapolated to all HPVs. Activated cell divisionis necessary for viral DNA access to the cell nucleus. Initial viral replication in the basal cells requires E1 and E2 proteins. The role of E6 and E7 in the basal layer is uncertain; particularly for the low-risk HPVs. Deregulation of E6/E7 expression is critical in determining neoplastic grade. In high-risk HPVs, E6/E7 mediates proliferation of the basal and parabasal cells, facilitating lesion growth. HPV E6 and E7 oncoproteins bind to and inactivate tumor suppressor proteins p53 and pRb, respectively, leading to malignant transformation of infected cells.

Transmission and natural history of HPV infection[26]:

HPV infection occurs at the basal epithelium during sexual intercourse. Although the incidence of infection is high, but most infections resolve spontaneously. Several studies have suggested that most women successfully clear the HPV infection, presumably through the action of a competent immune system. Among the infected individuals, approximately, 90% of lesions regress spontaneously without clinical signs or symptoms within 12 to 36 months, a small proportion of infected persons become persistently infected; which is the most important risk factor for the development of cervical cancer. The most common clinically significant manifestation of persistent genital HPV infection is Cervical Intraepithelial Neoplasia (CIN). Within a few years of infection, low-grade CIN(CIN 1) may develop, which may spontaneously resolve and the infection clear. Persistent HPV infection, may progress directly to higher-grade CIN (CIN2 or CIN3). High-grade abnormalities are at risk of progression to cancer. Some high-grade abnormalities spontaneously regress. If left, undetected and untreated, years or decades later CIN2 or 3 can progress to cervical cancer. The time lag between the peak of HPV infection and the peak of cancer incidence generally takes place over a period of 10 to 20 years, making the initiating infections and precursor lesions of cervical cancer anappropriate target for screening and early detection. Some lesions become cancerous more rapidly, sometimes within 2 years. Infection with one type of HPV does not prevent infection with another type. If persons infected with mucosal HPV, 5% to 30% are infected with multiple types of the virus.

HPV prevalence:

There have been many studies worldwide on the proportion of cervical cancer, other anogenital

cancers, high& low-grade squamous intraepithelial lesions (HSIL and LSIL) due to different HPV genotypes as well as prevalence of HPV in general population.

Bruni L et al[27] performed a meta-analysis of cervical HPV prevalence among women with normal cytological findings. The estimated global HPV prevalence was 11.7%. While based on the world regions Sub-Saharan Africa (24%), Eastern Europe (21.4%) and Latin America (16.1%) showed the highest prevalence's.

Alemany L et al[28] estimated the HPV type-specific distribution in a large series of invasive cervical cancer (ICC) over 70 years from 11 countries in Central-South America, Asia and Europe. Among 4,771 HPV DNA positive ICC cases, HPV16&18 were the two most common HPVs in all the decades (HPV16-from 61.5 to 62.1%, and HPV18-from 6.9 to 7.2%). A meta-analysis update conducted by SmithJS et al[6] showed HPV type distribution in ICCand HSIL. In ICC, HPV16 was the most common, and HPV18 the second most common, type in all continents. The next most common HPV types were HPV31, 33, 35, 45, 52 and 58. HPV18 was significantly more prevalent in adeno/adenosquamous carcinoma than in squamous cell carcinoma. Among HSIL cases, HPV16/18prevalence was 52%. WalboomersJM et al[3] found that the worldwide HPV prevalence in cervical carcinomas is 99.7%.

Bangladesh had also different studies that focused on HPV genotyping in different groups of females. Nahar Q et al[29] revealed prevalence of HPV infection was 7.7% with no significant difference between urban and rural women. HR-HPV (High risk) infections were more common (4.2%) than LR-HPV infections (3.4%). Most common HR genotypes were HPV16,66,18,45,31&53. Sultana T et al[30] noted the prevalence of genital HPV types in the sex workers was as high as 75.8%, whereas for the high-risk types it was 49.8%. The highest prevalence rate was observed for the genotype 16, 18 and 58. Khandker E et al[31] determine HPV infection rate was 43.1%. CIN cases had significantly high ($p<0.01$) HPV infection (78.6%) compared to cases with chronic cervicitis (18.2%).BanikU et al[7] find out the extent of HR HPV type 16/18 infection in women with epithelial cell abnormality in Pap smear. HPV type 16/18 infection was detected in 40.42% of the patients. Borna NN et al[8] identify HR HPV genotype among women having CIN and carcinoma. HPV 16 was detected in 81.82%followed by 18 in 9.09%& 45 in 6.06% cases of cervical carcinoma. Among precancerous cases, only type 16 was detected.

HPVprevalence in vulvar, vaginal and anal intraepithelial neoplasia (VIN, VAIN, AIN) grades 1-3 and carcinoma was conducted in 4 continents. Overall HPV prevalence was 67.8%, 85.3% and 40.4% among VIN1, VIN2/3& vulvar carcinomas; 100%, 90.1% and 69.9% among VAIN1, VAIN2/3& vaginal carcinomas; and 91.5%, 93.9% and 84.3% among AIN1, AIN2/3& anal carcinomas, respectively. HPV16 was found>75% and 18 <10% in HPV positive vulvar, vaginal and anal carcinomas. Approximately 40% ofvulvar, 60% of vaginal and 80% of anal carcinoma are responsible for HPV16/18.[32]

Co-factors associated with cervical cancer:

Muñoz N et al[5] stated that although HPV is a necessary cause of cervical cancer, it is not a sufficient cause. Epidemiologic studies indicate that the risk of contracting genital HPV infection and cervical cancer is influenced by a variety of factors. Thus, other cofactors are necessary for progression from cervical HPV infection to cancer. Long-term use of hormonal contraceptives, high parity, tobacco smoking, and co-infection with HIV have been identified as established cofactors; co-infection with Chlamydia trachomatis (CT) and herpes simplex virus type-2 (HSV-2), immunosuppression, and certain dietary deficiencies are other probable cofactors.

Strategies for cervical cancer prevention and control[33]:

WHO recommends a comprehensive approach to cervical cancer prevention and control. The recommended set of actions includes following interventions.

a) Primary prevention begins with HPV vaccination of girls aged 9-13 years, before they become sexually active. Because HPV vaccines do not protect against all HPV types that cause cervical cancer, vaccine introduction should be part of comprehensive approach to cervical cancer control.

Other recommended preventive interventions for boys and girls are:

- education about safe sexual practices, delayed start of sexual activity
- promotion and provision of condoms for those already engaged in sex

- warnings about tobacco use
- male circumcision.

b) Secondary prevention through screening and treatment of adult sexually active women for precancerous lesions, starting from 30 years of age.

c)Tertiary prevention and palliative care for women affected by invasive cervical cancer include surgery, radiotherapy and chemotherapy.

HPV vaccines[34]:
The availability of prophylactic HPV vaccines has provided a powerful tool for primary prevention of cervical cancer and other HPV-associated diseases. The vaccines are most effective when administered to a person prior to exposure to HPV. Two HPV vaccines are currently pre-qualified by WHO:

- A bivalent vaccine (Cervarix®, produced by GlaxoSmithKline)–protects against HPV 16 & 18 that cause the majority of cervical cancers; and
- A quadrivalent vaccine (Gardasil®/Silgard®, produced by Merck & Co)–protects against HPV 16 & 18, 6 & 11 that causes anogenital warts also.

As of December 2014, the U.S.FDA approved Merck's 9- valent HPV vaccine (GARDASIL 9®) which includes the additional five HPV 31, 33, 45, 52& 58 compared to the quadrivalent vaccine.

Both vaccines are composed of type-specific HPV L1 protein, the major capsid protein of HPV which is used as an antigen. Through Recombinant DNA technology the L1 protein undergoes conformal changes to self-assemble into 'virus-like' particles (VLPs). The VLPs are non-infective and non-pathogenic as these are devoid of the viral DNA essential to initiate the carcinogenic process. Bivalent vaccinecontains a novel adjuvant AS04 and quadrivalent vaccine VLPs are adsorbed on an aluminum-containing adjuvant to ensure robust and long-lasting immunogenicity.[12]

Table2 Summary of HPV vaccine characteristics

Attributes	Bivalent (Cervarix®)	Quadrivalent (Gardasil®/Silgard®)	9-valent (Gardasil 9®)
Vaccine type	Recombinant L1-capsid virus-like particles (VLP)	Recombinant L1-capsid virus-like particles (VLP)	Recombinant L1-capsid virus-like particles (VLP)
HPV types in vaccine	16,18	6,11,16,18	6,11,16,18,31,33,45,52,58
Disease protection	Cervical cancer (and premalignant genital lesions of cervix, vulva and vagina)	Cervical cancer (and premalignant genital lesions of cervix, vulva and vagina) Genital warts	Cervical cancer (and premalignant genital lesions of cervix, vulva and vagina) Genital warts
Cross-protection against HPV-types	31,33	31, 45	--
No. of doses	2	2	2
Dosing interval (flexibility)	0 and 6 months (No maximum interval but suggested not more than 12-15 months)	0 and 6 months (No maximum interval but suggested not more than 12-15 months)	0 and 6 months (No maximum interval but suggested not more than 12-15 months)
Method of administration	Intramuscular injection	Intramuscular injection	Intramuscular injection
Presentation and Type of Vaccine Vial Monitor (VVM)	1-dose vial; VVM 30 2-dose vial; VVM 30	1-dose vial; VVM 30	1-dose vial; VVM n/a
Shelf-life	48 months at 2-8 °C for 1-dose vial; 36 months at 2-8 °C for 2-dose vial; vaccine is freeze sensitive	36 months at 2-8 °C, vaccine is freeze sensitive	36 months at 2-8 °C, vaccine is freeze sensitive
Contraindications	-Severe allergic reaction to any vaccine component after first dose -Severe febrile illness -Known to be pregnant	- Severe allergic reaction to any vaccine component after first dose -Severe febrile illness -Known to be pregnant	- Severe allergic reaction to any vaccine component after first dose -Severe febrile illness -Known to be pregnant

(Adapted fromGuide to Introducing HPV Vaccine into National Immunization Programmes.2016)[34]

Mechanism of vaccine related protection:
Systemic immunization with L1 VLPs generates antibody concentrations higher than in a natural infection. The HPV vaccines are highly immunogenic leading to seroconversion in virtually 100% of vaccinees. Antibody titers in blood reach peaks 2–3 log higher than in natural infections, decrease gradually to levels several-fold lower than peak and then remain stable for years. The IgG is exuded at the possible sites of infection (mucosa of genital tract, oral cavity, etc.), neutralizes the virus and prevents its entry into the cells. The vaccine-induced immune memory in the form of circulating plasma cells and memory B-cells allows generation and exudation of protecting IgG each time the body is challenged by exposure to HPV infection. Animal models suggest that very low antibody titers may still be protective. Partial cross-protection against HPV31, HPV33 and HPV45 has been described.[25]

Recommended vaccination schedule:
The primary target group in most of the countries recommending HPV vaccination is young adolescent girls, aged 9-14.WHO has recommended the following vaccination schedule [35].

- Females <15 years at the time of first dose: a 2-dose schedule (0, 6 months) is recommended.

If the interval between doses is shorter than 5 months, then a third dose should be given at least 6 months after the first dose.

- Females ≥15 years at the time of first dose & immunocompromised and/or HIV-infected.: a 3-dose schedule (0, 1-2, 6 months) is recommended.

Evaluation of efficacy, immunogenicity and safety of HPV vaccine:
HarperDM et al[36] assessed the long-term efficacy, immunogenicity, and safety of a bivalent HPV-16/18 L1 virus-like particle AS04 vaccine against incident and persistent infection with HPV 16 & 18 and their associated cytological and histological outcomes. De Carvalhoa N et al[37] report efficacy and immunogenicity of the HPV16/18 vaccine up to 7.3 years post vaccination. No cases of infection or cytohistological lesions associated with HPV 16/18 were observed in the vaccinee. Another follow up study (up to 4 years) of SchwarzTF et al[38] showed persistence of immune response to HPV-16/18 vaccine in women aged 15–55 years. All subjects were seroconverted for anti-HPV-16&18 antibodies at Month 7. At Month 48 of that study, all subjects were still seropositive for anti-HPV-16 antibodies and all but one subject in the 46–55 years age group remained seropositive (99.4%) for anti-HPV-18 antibodies. Roteli-Martins CM et al[39] report the long-term efficacy and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine up to 8.4 y after the first vaccine dose. No new infection or lesions associated with HPV-16/18 occurred in the vaccine group. NaudPSet al[19] conducted a long-term follow-up of an initial double-blind, randomized (1:1), placebo-controlled study evaluating the efficacy against HPV16/18 infection and associated cyto-histopathological abnormalities, persistence ofimmunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine. No new HPV 16/18-associated infections and cyto-histopathological abnormalities occurred in the vaccine group.

Khatun S et al[18] conducted a study to assess the immunogenicity and safety profile of HPV16/18 vaccines in healthy Bangladeshi girls aged between 9–13 years. They recommended that, bHPV vaccine was generally well tolerated, with no vaccine-related serious adverse effects.

HPV prevalence, cross-protection and herd immunity after vaccination:
A national HPV immunization program using a bHPV vaccine was implemented in Scotland in 2008, along with a national surveillance program designed to determine the longitudinal effects of vaccination on HPV infection at the population level. By linking vaccination, cervical screening, and HPV testing data, over the study period they found a decline in HPV 16 &18,significant decreases in HPV 31, 33& 45 (suggesting cross-protection). Among non-vaccinated women, HPV 16 & 18 infections were significantly lower in 2013 than in 2009 indicating herd immunity and sustained effectiveness of the bivalent vaccine onvirologic outcomes at the population level.[17]

Scenario of HPV vaccination in Bangladesh:
WHO has developed guidelines on prevention and control of cervical cancer through vaccination and screening. By mid-2016, globally 65 countries, mostly in high-income and upper-middle-income settings had introduced HPV vaccines into their national immunization programs[33]. But the global burden of cervical cancer fallsheaviest on the

developing countries which haven't introduced the HPV vaccine as part of their national public health strategy to prevent and control cervical cancer.

Bivalent HPV vaccine was registered in Bangladesh in 2009 while qHPV was registered in 2014.HPV vaccine has recently been introduced in Bangladesh by the Ministry of Health and Family Planning (MoHFP), with support from the Global Alliance for Vaccines and Immunizations (GAVI). This new vaccine introduction program ran for two years in Gazipur district and if it is successful, GAVI will provide support for national introduction of HPV vaccine[40]. WHO recommends that girls are vaccinated with HPV vaccine between the ages of 9-13 years. In line with this, the Government of Bangladesh has decided to vaccinate 10-year-old girls in the primary school setting (Grade 5) with two doses of bHPVvaccine, given 6 months apart. The target girls will mainly be reached through the schoolbasedprogramme and girls who are out of school will receive the vaccine through the routine EPI sites at the community level.

Conclusion:

Immunization with the HPV vaccine induces sustained high levels of antibodies against high-risk HPV genotypes 16 and 18. The durable immune response induced by the HPV vaccine in adolescent girls is predicted to provide long-term protection against HPV infection and subsequent development of high-grade cervical lesions and cancer. The knowledge gained from this review is important for realizing the necessity of the use of a prophylactic HPV16/18 vaccine in Bangladeshi girls. There has been little success with screening program against cervical cancer in Bangladesh, an intervention that has helped to significantly reduce cervical cancer in the developed world. Therefore, a National HPV Vaccination Program seems to be the window of opportunity to reduce the mortality and morbidity of HPV related cervical cancer in Bangladesh.

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