

## Human Papillomavirus Vaccine: the Beginning of the End for Cervical Cancer\*

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**Key words:** human papillomavirus, cervical cancer, vaccine, cervical intraepithelial neoplasia, *Condylomata acuminata*

### Abstract

The human papillomavirus family of viruses causes a variety of benign, premalignant and malignant lesions in men and women. All cervical cancers are caused by HPV. It is the leading cause of death from cancer in women in developing countries; every year some 493,000 women develop cervical cancer and 230,000 die every year from this disease. The vaccine against HPV includes virus-like particles, composed of the major viral capsid protein of HPV without the carcinogenic genetic core. Large-scale studies have shown that the vaccine is tolerated well, leads to high antibody levels in both men and women, and prevents chronic HPV infection and its associated diseases. To achieve effective coverage the vaccine should be given prior to sexual debut. Introduction of the vaccine into specific countries, particularly Israel, should take into account the local incidence of cervical cancer as well as the increasing incidence of precancerous cervical lesions and genital warts, which reduce quality of life and are associated with considerable costs.

*IMAJ 2007;9:156-158*

Research and development of human papillomavirus vaccine started in 1993, but it was not until 2002 that it attracted the attention of the general medical community [1]. At that time the first large-scale phase II study was published, demonstrating the effectiveness of HPV vaccine in preventing persistent HPV infection and development of cervical intraepithelial neoplasia, the precancerous cervical lesion. It immediately initiated a flood of interest in the new possibilities for the prevention of cervical cancer.

One of the reasons for the delay in developing the vaccine is that for years it seemed unsafe to introduce attenuated or extinct virus into the human body, if there was a chance of its DNA causing a malignant transformation. The turning point came in the 1990s with the development by Ian Frazer of a virus-like particle consisting of a viral capsid without DNA, which forms the structure of the HPV vaccine [2]. In addition, the recognition beyond any doubt that HPV is indeed the causative agent of cervical cancer has grown since the 1980s [3,4]. Advances in molecular biology methods have confirmed this correlation.

### Characteristics of the virus

HPV is a non-enveloped DNA virus and is a member of the papillomaviridae family. It is coated by a 72-sided icosahedral capsid. Its double-stranded DNA is circular and comprises approximately 7900 nucleotide base pairs [5]. The genome is composed of two

regions: the "early" region that contains six open reading frames encoding for early proteins (E1, E2, E4, E5, E6 and E7) that control viral replication, transcription and cellular transformation; while the late region encodes for a large nucleocapsid protein L1 and a small L2 of the capsid. These sequences are highly conserved among all papillomaviruses.

More than 100 types of papillomaviruses are known to infect humans. Each of the HPV types differs by more than 50% in their nucleotide sequences. Approximately 35 types are known to infect the genitalia. These types are divided into groups based on the frequency of association with malignant tumors and their oncogenic potential. A high risk genital type is an HPV that may be associated with advanced precancer or cancer. The high risk HPV types are: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82 [5]. The low risk types are 6, 11, 26, 42, 44, 54, 70 and 73. They are associated with *Condylomata acuminata* of the genital tract.

Infection by HPV results in the maintenance of the genome as a viral episome in the nucleus of the infected cell, independent of the host cell genome. Infrequently, the circular episome genome breaks at the region of the E1-E2 region, leading to integration of the viral DNA into the host genome. The break of the E2 gene is significant because the E2 gene product regulates transcription of the HPV genome. Its disruption leads to an increase in the production of E6 and E7 gene products [6]. This excess production of E6 and E7 proteins initiates the carcinogenic process, as these proteins bind to and inactivate the tumor suppressor gene products p53 and retinoblastoma protein respectively.

### Magnitude of HPV-associated disease

HPV is associated with a variety of benign, premalignant and malignant conditions: *Condylomata acuminata* (genital warts) on the vulva, perineum, perianal area, vagina or cervix in women, and the penis or scrotum in men, are caused by infection with HPV types 6 and 11 [5]. Neonatal infection with HPV 6 or 11 may lead to development of respiratory papillomatosis in the neonatal larynx – laryngeal papillomatosis. HPV 16 and 18 as well as other high risk types cause premalignant conditions, such as cervical, vaginal, vulvar and perianal intraepithelial neoplasia, and malig-

\* Presented at the 18th Israeli Medical Association World Fellowship International Conference  
HPV = human papillomavirus

nant diseases such as cervical, vulvar, vaginal, anal and perianal cancers. HPV types 16 and 18 are associated with 70% of cervical cancers and HPV 6 and 11 with 90% of genital warts. Cervical cancer is the leading cause of cancer-related mortality among women in developing countries, accounting for approximately 230,000 deaths per year [7].

HPV infection is a common sexually transmitted disease, with maximum cumulative prevalence rates of up to 82% being reported in sexually active adolescents [8]. Each year, an additional 300 million people are infected with HPV, of whom 30 million develop *C. acuminata*. Most HPV infections are transient and resolve within a couple of years. For a lesion to progress to neoplasia, the HPV infection must be persistent.

The initial significant consequence of persistent HPV infection is usually a low grade cervical premalignant cervical lesion – cervical intraepithelial neoplasia grade 1. Each year, 30 million women develop CIN-1. In up to 33% it may progress to a high grade lesion – CIN-2 or CIN-3. Ten million women are diagnosed yearly with CIN-2 and CIN-3 [2].

The transit time of an untreated high grade lesion to cervical cancer is variable, ranging from a few months to a few decades. Every year cervical cancer is diagnosed in 493,000 women worldwide. The incidence of cervical cancer varies around the world; it is 8/100,000 women in the United States and 6/100,000 in Israel. The disease can be detected in the precancerous stages of development by a screening system involving cytological cervical sampling by a Pap smear. Women with an abnormal smear are referred to a colposcopy clinic where the precancerous lesion is examined through optical equipment, biopsies are taken, and the involved portion of the cervix is excised using a diathermy loop [8].

## Principles of vaccine production

Two types of vaccine have been developed: prophylactic and therapeutic. Therapeutic vaccines are targeted against the E6 or E7 HPV genes, but none have yet reached a clinical stage. The prophylactic vaccine aims at preventing primary persistent infection and is targeted against the L1 gene product, which is the major protein of the HPV capsid. Vaccine development began in the early 1990s, after the gene encoding for the HPV envelope protein L1 was isolated. This gene was then inserted into the DNA of the yeast *Saccharomyces cerevisiae* to create a recombinant DNA. The yeast then expressed the L1 capsid protein [9] and produced the L1 protein that spontaneously assembles into a virus-like particle. The VLP resembles the native HPV virus, but lacks the DNA core. Therefore, it does not carry any infectious or carcinogenic risk. The commercial vaccine contains the 97% purified VLP adsorbed onto an aluminum adjuvant, which varies among the pharmaceutical companies. The human

immune system recognizes the VLP as if it were HPV itself, thus producing a neutralizing antibody response.

## Prophylactic vaccine trials

HPV-VLP vaccines are highly immunogenic even at low antigen doses, and induce the HPV type-specific serum antibody levels some 100 times higher than those achieved after natural infection. The serum antibodies are excreted onto the cervical epithelium [10] and protect against a genuine HPV infection.

The initial efficacy study published in 2002 evaluated a vaccine aimed at inducing immunity against HPV-16 (Merck Research Laboratories, West Point, PA, USA) [1] [Table 1]. The vaccine indeed showed 100% efficacy in preventing persistent HPV 16 infection. No serious adverse events occurred in either the vaccine or the placebo groups. A 3.5 years post-vaccination follow-up of the same study was then published, confirming a vaccine efficacy of 100% (95% confidence interval 65–100%) [11]. One of the criticisms against the 2002 publication was that developing a vaccine against only one type of a high risk HPV type is insufficient. Hence, further development of HPV vaccines involved preparations against more than one type.

A randomized, double-blind, placebo-controlled trial using bivalent HPV 16/18 VLP preparation – Cervarix™ (GlaxoSmithKline, PA, USA) was successful [12]; the vaccine proved to be 100% effective against persistent infection with HPV 16, 18, or both. There were no serious adverse events related to vaccination. An additional benefit of this vaccine was the unintended development of antibodies against HPV 31, 45 and 52 in vaccine recipients, referred to as “cross-immunity,” offering protection against an additional 10% of cervical cancer carcinogens. The cross-immunity was attributed to the ASO4, the enhanced adjuvant used in the bivalent vaccine preparation. Subsequently, a quadrivalent VLP vaccine against HPV types 6, 11, 16 and 18 (GARDASIL™, Merck) was also tested in several randomized, double-blind, placebo-controlled multicenter trials [13]. It showed 100% efficacy against persistent HPV infection and against the development of CIN-1, 2 and 3. There were no discontinuations for serious vaccine-related adverse events. The most common minor vaccine-related adverse event reported was local discomfort at the injection site. Table 1 summarizes the results of the major multicenter studies with the various vaccines [1,11-17]

**Table 1.** Results of studies with various HPV vaccines

	Harper 2006 [15]	Harper 2004 [12,16]	Munoz 2006 [14]	Koutsky 2005 [17]	Villa 2005 [13]	Koutsky 2002 [11], Mao 2006 [11]
Vaccine valency	Bivalent	Bivalent	Quadrivalent	Quadrivalent	Quadrivalent	Monovalent
HPV type	16/18	16/18	6/11/16/18	6/11/16/18	6/11/16/18	16
Size of trial	393 vaccine, 383 placebo	560 vaccine, 553 placebo	241	5301 vaccine, 5258 placebo	239 vaccine, 242 placebo	768 vaccine, 765 placebo
Age (yrs)	15–25	15–25	16–23	16–23	16–23	16–23
Duration	4.5 yrs	27 mos	5 yrs	48 mos	48 mos	48 mos
Efficacy prevention	100	100	100	100	100	100
CIN-2 3 (%)	(0 vs. 10)		(0 vs. 6)	(0 vs. 21)		(0 vs. 12)
Seroconversion (%)	98	100	100	100	100	100

CIN-1 = cervical intraepithelial neoplasia grade 1  
VLP = virus-like particle

## Target groups

The ideal age for vaccine administration is prior to sexual debut in order to maximize efficacy prior to a primary encounter with HPV types. Men would be expected to benefit from a vaccine that prevents anal cancer, penile cancer and genital warts. In addition, the vaccinated men would maximize the public health impact of HPV vaccines by herd immunity [18]. Vaccine implementation may have implications for existing cervical cancer screening protocols. The vaccine contains VLPs of HPV genotypes that account for approximately 70% of cervical cancers. Thus, women must understand that they should continue to participate in Pap screening even after vaccination.

## Vaccine acceptability

Objection to vaccination of children and adolescents by HPV vaccine may exist at various levels [19]. Parents may be reluctant to consent to immunization of their children against a sexually transmitted disease because they do not believe that their child is at high risk for these infections; they may not be willing to initiate a discussion about sexuality or sexually transmitted diseases, or they may be concerned that adolescents who are vaccinated would practice riskier sexual behaviors. At the physician level, clinicians may be reluctant to discuss issues of sexual activity and sexually transmitted diseases with children and early adolescents. Religious circles do not publicly acknowledge that sexual activity occurs outside of marriage, or that it may occur at an early age.

A major consideration at the present time, which will determine the rate of introduction of the vaccine to any given country, is cost-effectiveness [20]. In Israel, although the vaccine is expensive, calculations should take into account that it prevents not only cancer of the cervix, vulva and vagina, but also precancerous lesions and condylomata, which require unpleasant and expensive treatment. Furthermore, less than a decade after its introduction, it will preclude the need for periodic cervical screening, with its accompanying expenses, in the investigation of women with abnormal Pap smear tests.

## Conclusions

Prophylactic HPV vaccines can substantially reduce the morbidity and mortality associated with cervical cancer and other HPV-associated diseases. Evidence from trials of prophylactic HPV vaccines suggests that they are well tolerated, highly immunogenic, and prevent the acquisition of both HPV infection and HPV-related disease.

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