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DIPLOMA THESIS

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CHARLES UNIVERSITY IN PRAGUE

FACULTY OF PHARMACY IN HRADEC KRÁLOVÉ

Department of Social and Clinical Pharmacy

QUADRIVALENT HUMAN PAPILLOMA VIRUS VACCINE

Evaluation of clinical effectiveness and national vaccine programs

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HRADEC KRÁLOVÉ 2008 **NATAŠA LEKIĆ**

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This work is dedicated to my family, my mother Slobodanka, my father Goran and my sister Andrea. Thank you for believing in me and helping me achieve my goals.

I, Nataša Lekić, declare that this work is my original author's work and that all the information resources are presented in the list of references.

Hradec Kralove, May 22nd, 2008 Nataša Lekić

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INTRODUCTION

Human pappillomaviruses (HPV) are group of DNA viruses that infect ano-genital tract. HPV types 16 and 18 are found in majority of HPV infections and are also termed 'high-risk' types. Persistent infection by these high risk HPV types is a major cause of development of cervical cancer, which annually infects one million women worldwide. Low risk HPV types are 6 and 11 are major causes of genital warts, which are another health problem due to a HPV infection.

The widespread national cervical cancer screening programs using Pap testing have reduced the incidence and mortality of cervical cancer in developed countries. Despite this, the disease still kills several hundred thousand women per year worldwide and is a major problem in many nations. The key role of HPV infection in the etiology of cervical cancer provides an opportunity to control this cancer through immunization against the most common high risk HPV types.

Merck co. has recently launched a quadrivalent HPV vaccine Gardasil/Silgard, which is aimed to prevent infection with HPV types 6, 11, 16 and 18. Clinical trials have been designed to evaluate efficiency and safety of this vaccine in large scale populations. The information from these trials is crucial for government's decisions regarding implementations of the vaccination programs and assessment of cost-benefit analysis. These evaluations have become an important source of information to aid in decision making about the allocation of the resources.

The Canadian government has introduced a preventive, voluntary, government funded HPV quadrivalent vaccine (Gardasil) programs which are aimed at reducing the occurrence of cervical cancer among the female population. This will be used as an example for government's allocation of resources using the cost-effectiveness approach and introduction of guidelines.

AIM OF STUDY

The aim of this summarized study is the evaluation of effectiveness, safety and the economical value of quadrivalent HPV 6/11/16/18 vaccine (Gardasil/Silgard) manufactured by Merck co. This study was performed using bibliographical investigation of various scientific databases, government publications and manufacturer's publications.

In theory, after analyzing the data of the new vaccine obtained from clinical trials it is possible to determine benefits of introducing national vaccination programs. Evaluation of the vaccine is determined by the balance between its effectiveness and its safety in comparison to standard preventive therapy. This evaluation should be used on a national level in the process of introducing the new vaccine into immunization program. It allows decision regarding reimbursement costs of vaccine and funding of national vaccination programs, by allocating resources and identifying the target population. Canada has been chosen as an example of implementation of successful Gardasil/Silgard vaccination programs among young women. Various crucial factors for implementation of successful HPV vaccination programs at the national level are included in the assessment.

METHODOLOGY

Publications in this diploma thesis were primarily identified through Medline and PubMed searches and from citations from identified publications. Search terms included "papillomavirus, human", "cost-benefit analysis", "cost-effectiveness analysis", "HPV vaccination programs", "HPV vaccine", "cervical cancer" and " genital warts". Publications included mainly journals, published articles and guideline manuals.
All of the searches were filtered for English language and date of publication from 2000 to 2008.

The approach for the background information included the information obtained from the following sources

- Information on cervical cancer, HPV infection and related diseases from World Health Organization (WHO), Canadian Cancer Society, American Cancer society, European Agency for the Evaluation of Medicinal Products (EMEA)
- Information regarding HPV quadrivalent vaccine (Gardasil/Silgard) from the manufacturer Merck Co.
- Various journals searched from Medline and Pubmed.

The approach for the information regarding clinical trials was obtained from

- WHO and EMEA
- Information published by Merck Co.

Final part of the diploma thesis regarding pharmacoeconomics included the information obtained from following sources

- Various journal articles obtained from Pubmed searches, prominently Vaccine Journal.
- Publications from WHO, EMEA and Ministry of Health Canada.

I. BACKGROUND

1. INTRODUCTION

HPV infection, caused by human pappillomavirus, is one of the most common causes of sexually transmitted disease in both men and women worldwide [5].

Human papillomaviruses are a group of DNA viruses that infect the skin and mucous membranes of humans. These are virus particles consisting of circular DNA molecules wrapped in a protein shell. The shell is made up of two protein molecules, L1 and L2. More than a hundred different types have been identified. Some of them may cause warts while others may cause a subclinical infection resulting in precancerous lesions. All HPVs are transmitted by direct skin-to-skin contact. A large number of these viruses are transmitted sexually and tend to infect anogenital region. This infection can be asymptomatic, but it mostly manifests itself by genital warts caused by HPV types 6 and 11. These are classified as low risk (LR) for causing cancer, but cause the majority of genital warts. Studies have shown that almost all cervical cancers can be traced to infection with oncogenic HPV types 16 and 18. These types are referred to as high risk (HR) because of their link to cervical cancer. Persistent infection with high risk types of human papilloma viruses can lead to premalignant lesions, which tend to progress to cervical cancer. It is known that HPV infection is a preliminary step in development of almost all cases of cervical cancer [3,4].

The new quadrivalent HPV (6,11,16,18) vaccine (Gardasil/Silgard) aims to prevent infection by these most common LR and HR HPV types.

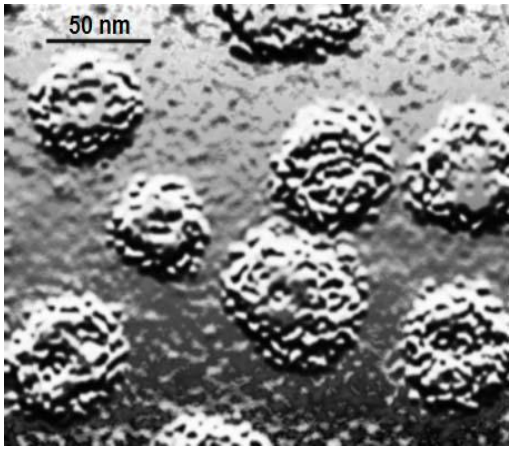
2. HUMAN PAPILLOMAVIRUS (HPV)

The epithelial lining of the anogenital tract is the target for infection by human papillomaviruses. They tend to cause clinical genital warts, also known as *condylomata acuminata*, and nearly all squamous cell cancers of the anogenital tract [1].

2.1. HPV Virology

Human papillomaviruses are small, non-enveloped, ssDNA viruses that are members of the *Papovaviridae* family. They are 55 nm in diameter and have an icosahedral capsid composed of 72 capsomers, which have two capsid proteins, L1 and L2. Each capsomer is a pentamer of the major capsid protein, L1. Each virion capsid contains several copies of the minor capsid protein, L2. The following picture illustrates the complex structure of these viruses.

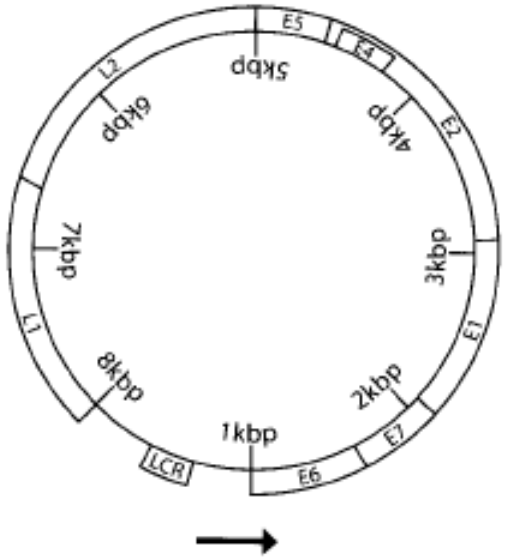
Picture 1- *Electron Microgram of Pappilomavirus. The size and shape of Pappilomavirus can be seen in this electron microgram, where uneven coating shows capsid proteins.*



***Source**: EM of pap virus, basal tissue grafted to mouse. http://en.wikipedia. org/wiki/HPV_virus*

The HPV genome consists of a single molecule of double-stranded, circular DNA and is functionally divided into three regions. The first is a non-coding upstream regulatory region that is highly variant and contains the p97 core promoter along with enhancer and silencer sequences that regulate DNA replication by controlling the transcription of the open reading frames. The second is an early region, consisting of open reading frames E1, E2, E4, E5, E6, and E7, which are involved in viral replication and oncogenesis. The third is a late region, which encodes the L1 and L2 structural proteins for the viral capsid [5]. The following picture is a schematic representation of the HPV DNA genome.

Picture 2 - *Circular HPV DNA genome. Early and late regions of circular DNA are shown with their respective size in kilo base pairs (kbp)*



Source: *Burd E.M.. Human papillomavirus and cervical cancer. Clinical Microbiology Reviews 2003; 16 (1) 1-17*

Defined by the basis of DNA homology there are more than one hundred HPV types, of which more than forty infect the anogenital tract. HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 are considered to be of high risk (HR) of causing cancer. The remaining genital types 6, 11, 42, 43 and 44 are considered of low or no oncogenic risk (LR) [1,14].

The following table summarizes some notable HPV types and associated diseases that they cause [5]

Table 1- *Anogenital diseases caused by respective HPV types*

Disease	**HPV type**
Anogenital warts	**6**, **11**, 42, 43, 44, 55
Recurrent respiratory papillomatosis	**6, 11**
Conjuctival papillomas/carcinomas	**6, 11, 16**
Condyloma acuminate (genital warts)	**6, 11,** 30,42, 43, 45, 51, 54, 55, 70
Cervical intraepithelial neoplasia	
Low risk	**6, 11, 16, 18,** 31, 33, 35, 42, 43, 44, 45, 51, 52, 74
High risk	**16, 18, 6, 11,** 31, 34, 33, 3, 53, 42, 44, 45, 51, 52, 56, 58, 66
Cervical carcinoma	**16, 18,** 31, 45, 35, 39, 51, 52, 56, 58, 66, 68, 70

Source: *Muñoz N., Bosch X.B, Sanjosé S. & authors. Epidemiologic classification of human papillomavirus types associated with cervical cancer. The New England Journal of Medicine 2003 ; 348 (6) 518-527.*

2.2. HPV INFECTION

2.2.1. Incidence & Prevalence

It is estimated that HPV prevalence among women around the world ranges from 2% to 44%, depending on the geographic region, population sampled and testing methodology. However, there is consistency among results that shows a peak prevalence of HPV infection in women younger than 25 years, with a decreasing prevalence with increasing age [4]. There is a sharp decrease in prevalence after 30 years of age. However, cervical

cancer is more common in women older than 35 years, suggesting infection at a younger age and slow progression to cancer [5,12].

The International Agency for Research on Cancer's multi-center cervical cancer studies have shown that, around the world, HPV type 16 is the most prevalent; It accounts for 54.6% of HPV-infected patients with squamous cell cervical cancer. Types 16, 18, 45, 31 and 33 accounted for 80% of the type distribution in squamous cell carcinomas, and types 16, 18, 45, 59 and 33 accounted for 94% of the type distribution in adenocarcinomas [4]. The greatest risk of HPV infection coincides with greatest metaplastic activity, which occurs at puberty and first pregnancy and declines after menopause [5].

Despite the fact that HPV infection is the most common sexually transmitted infection, it is not a nationally recognized disease in most countries. Currently there are no population-based studies that have been published. Canada has been used as an example of an industrialized nation with excellent available statistical data regarding HPV infection. The following summarized studies are estimates of HPV infection that are based on Canadian prevalence and incidence studies in select populations, such as patients in routine cervical screening clinics, family planning clinics, STI/HIV clinics and university health clinics. All published Canadian studies have been conducted in women only. Within Canada, the overall prevalence of any HPV type ranges from 10.8% to 29.0% and it appears to vary with age, place of residence and ethnicity. The age group most infected with HPV is seen in young adults around the age of 25 years. Concerning ethnicity, the highest rates of high risk HPV infection accounting for 86% of female population and the youngest age of HPV infection are seen in Inuit . There is a high prevalence in ages 13 to 20 years, with 31.7% in Inuit versus 11.8% in the rest of the population. Higher rates of infection seen in Inuit populations are due to lower socio-economic status, thus Inuit women do not have regular access to health care and sex education as the rest of the Canadian population [4].

Few studies in female population have been conducted regarding the HPV incidence in Canada. One prevalence study involved Ontario women with a follow-up study 1 year

later. Among those 15 to 49 years of age (mean 32.7 years) with a mean interval of 14 months of follow-up, incident high risk HPV infection was found in 11.1% of women who were initially HPV negative. The highest incidence was found among those aged 15 to 19 years (25.0%), followed by those 30 to 34 years (14.7%) [6].

Risk of HPV infection is high following sexual debut. In a study of Canadian female university students the cumulative incidence of HPV infection in those initially tested to be HPV negative was on average 38.8% in 24 months of follow-up for those who were sexually active at enrollment and for those who were virgins. Incident infection with HPV type 16 was 10.4% and with HPV type 18 was 5.6% [4].

2.2.2. Pathogenesis

Human papillomaviruses can infect basal epithelial cells of the skin or inner lining of tissues. They are categorized as cutaneous types of HPV, which are epidermotrophic and target the skin of the hands and feet. On the other hand, mucosal types infect the lining of the mouth, throat, respiratory tract, or anogenital epithelium [5]. These infections are transmitted sexually by direct skin contact, as well from a pregnant mother to her child. Transmission from oral mucosal contact in head and neck infections has also been documented.

The virus enters the epithelium through a break, infecting and replicating in basal and parabasal cells. In this case the virus is established as an episome in the human cell's nucleus. As these cells mature, translation of viral genome occurs with assistance from the host cell machinery. This results in the creation of progeny virus, which are then shed at the epithelial surface.

HPV replication cycle begins with an entry of the virus into the cells of the basal layer of the epithelium through a break in the skin. Integrin has been proposed as the epithelial cell receptor for HPV-6, while heparin sulfate is for HPV-16 type. The uptake mechanism has not yet been established, however once inside the host cell, HPV DNA

replicates as the basal cells differentiate and progress to the surface of the skin. In the basal layers, viral replication is considered to be non-productive and the virus establishes itself as a low-copy-number episome by using the host DNA replication mechanisms to synthesize its DNA. In the differentiated keratinocytes of the upper layers of the skin the virus replicates and amplifies its DNA to high copy number, synthesizes capsid proteins, and causes viral assembly to occur.

HPVs must use host cell factors to regulate viral transcription and replication. Their replication begins with host cell factors that interact with the LCR region of the HPV genome and begin transcription of the viral E6 and E7 genes (see picture 2, pg. 11). These gene products disrupt the host cell growth cycle by binding and inactivating tumor suppressor proteins, cell cyclins, and cyclin dependent kinases. They also weaken the cell growth-regulatory pathways and make cellular environment most beneficial for viral replication, resulting in continuous proliferation and delayed differentiation of the host cell.

The E1 and E2 gene products are synthesized and the E2 gene blocks transcription of the E6 and E7 genes and allows the E1 gene product to bind to the viral origin of replication located within the LCR. This binding starts replication of the viral genome as extra-chromosomal elements in the S phase of the cell cycle. As a result, the release of the p53 and pRB proteins occurs, and the normal differentiation process of the host continues. This is followed by activation of capsid genes L1 and L2 by a putative late promoter. Viral particles are assembled in the nucleus, and complete virions are released as the cornified layers of the epithelium are shed [5].

2.2.3. Clinical Manifestations

Most HPV infections are benign. HPV infection with types 6 and 11, can result in anogenital warts, which are typically warty projections that can occur anywhere in the genital skin surface but primarily on the vulva, penis and perianal skin. They are mostly self limited lesions in immuno-competent individuals, resolving typically in 1-2 years. It is estimated that HPV 6 and 11 cause 90% of genital warts [4].

Asymptomatic cervical HPV infection can be detected in 5%–40% of women of reproductive age. HPV infection is transient, because only a small proportion of women positive for a given HPV type are found to have the same type in following tests. Risk of subsequent cervical intraepithelial neoplasia (CIN) is proportional to the number of specimens testing positive for HPV, which suggests that carcinogenic development results from persistent infections. Recent tests by polymerase chain reaction (PCR) of a large international collection of cervical cancer specimens has shown that HPV DNA is present in 99.7% of cases. This clearly shows that HPV infection is a necessary cause of cervical neoplasia [1].

HPV has also been implicated in the much more rare cancers of the penis, anus, vulva and vagina, in which mechanisms of oncogenicity are presumed to be similar to those of the cervix, but the rapidly replicating nature of the cervical transformation zone appears to make this area more susceptible to its oncogenic influences [4].

Other notable diseases caused by various HPV types include; Focal epithelial hyperplasia of the oral cavity (Heck's disease) is caused predominantly by HPV-13 and also regressess spontaneously. Epidermodysplasia veruciformis is a rare genetic disease with HPV-associated warts on the chest and upper extremities, which can develop into invasive squamous cell carcinomas. Recurrent respiratory papillomatosis is a disease of the larynx in young children, which is thought to be acquired by passage through an infected birth canal. This disease can also occur in adults and the lesions may undergo malignant transformation. It is caused by HPV types 6 and 11.

3. CERVICAL CANCER

Cervical cancer is the malignant cancer of the cervical area. The human papillomavirus infection is the major cause of cervical cancer. The symptoms appear in advanced stages, and it has been focus of intense screening efforts using the Pap smear. Prevention programs are aimed at vaccinating young girls with quadrivalent HPV vaccine. Treatment includes cancerous tissue excision procedures.

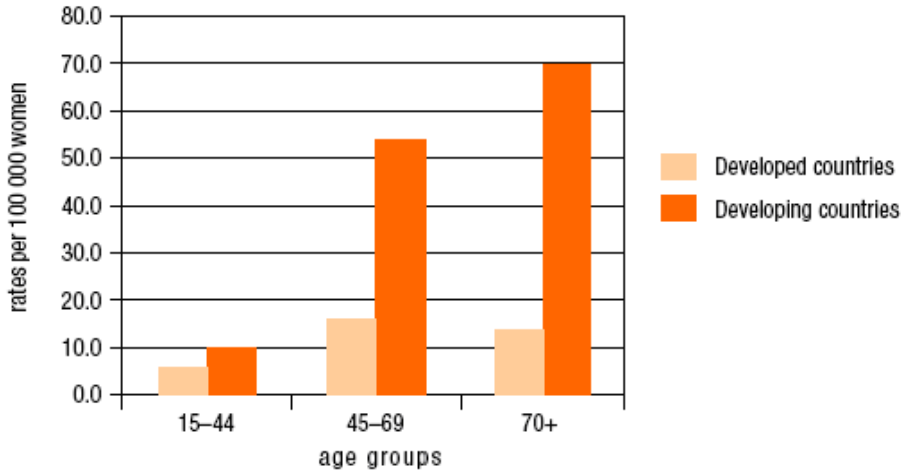
3.1 Incidence, Prevalence & Mortality

Globally, cervical cancer is one of the most common causes of cancer death in women. It represents nearly 10% of all cancers in women. [2]. In frequency, it is the third among women, after breast and colorectal cancer. In general, there is a correlation between incidence and mortality across all regions of the world, with the mortality rate in Canada being one of the lowest [1]. Once again Canada will be used as an example of a developed nation dealing with burden of cervical cancer caused by HPV infection.

According to World Health Organization (WHO) in the year 2005 there were estimated 500 000 new cases of cervical cancer world-wide, of which over 90% were in developing countries. It is estimated that over one million women in the world currently have cervical cancer, most of whom have not been diagnosed, or have no access to treatment. In 2005, mortality reached 260 000, nearly 95% of women in developing countries, making it one of the serious threats to women's lives[7]**.**

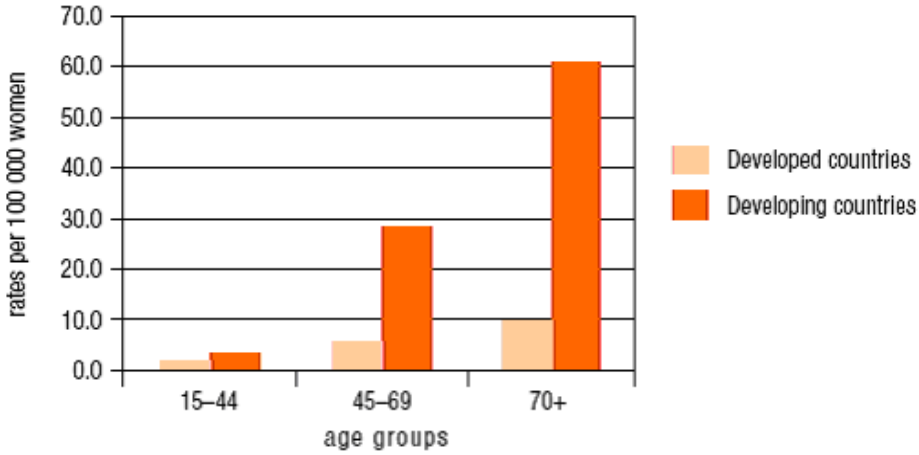
Population-based data have shown that the incidence of genital HPV infections, including infections with low risk types, decreases with age. Thus, detection of HPV infection among older women is more likely to reflect persistent infection, whereas detection among younger women more often represents recently acquired and probably transient infection [7,10,12].The following two figures illustrate incidence and mortality rates of cervical cancer in developed and developing countries according to age distribution.

Graph 1- *Age standardized incidence rates of cervical cancer in developed and developing countries in 2005. The graph shows the highest incidence of cervical cancer to be among women 70 years and older, while those younger than 44 years are at the lowest risk.*



Source: *World Health Organization (2006) Comprehensive cervical cancer control: A guide to essential practice. ISBN 978 92 4 154700 0*

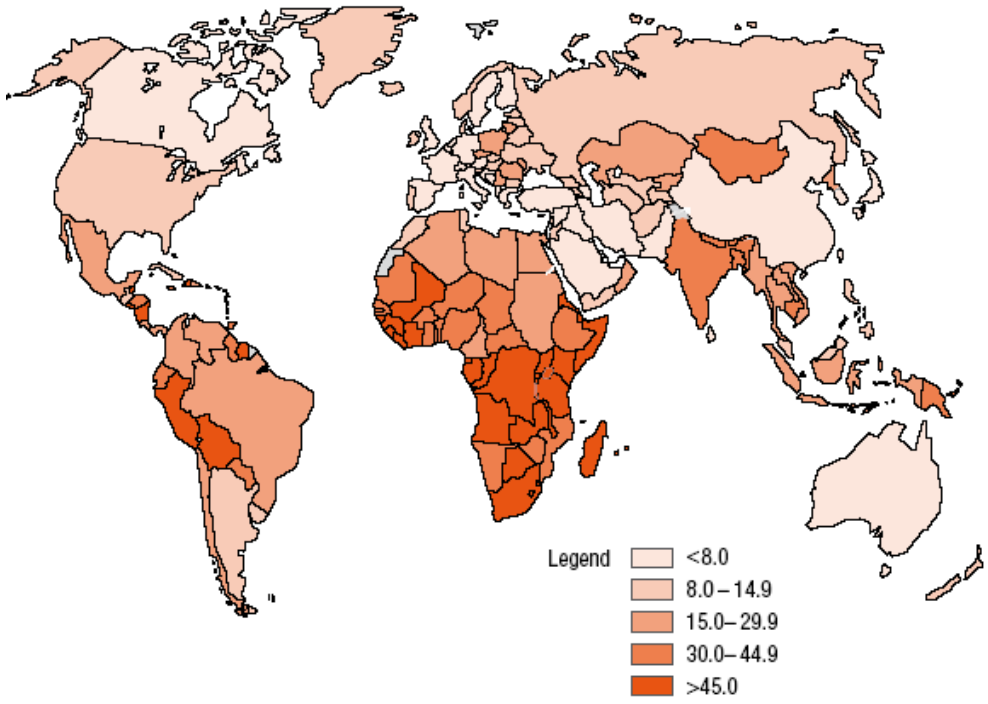
Graph 2- *Age standardized mortality rates of cervical cancer in developed and developing countries in 2005. From this graph it can be seen that mortality rates due to cervical cancer are highest among women older than 70 years of age, while mortality is significantly lower in younger age groups.*



Source: *World Health Organization (2006) Comprehensive cervical cancer control: A guide to essential practice. ISBN 978 92 4 154700 0*

Cervical cancer occurs worldwide, but the highest incidence rates are found in Central and South America, eastern Africa, South and South-East Asia, and Melanesia. The following figure shows the global incidence distribution of cervical cancer.

Picture 3- *Worldwide incidence rates of cervical cancer per 100,000 females (all ages) age-standardized to the WHO standard population in 2005. Highest incidence rates are among developing countries, while the lowest being in developed nations.*

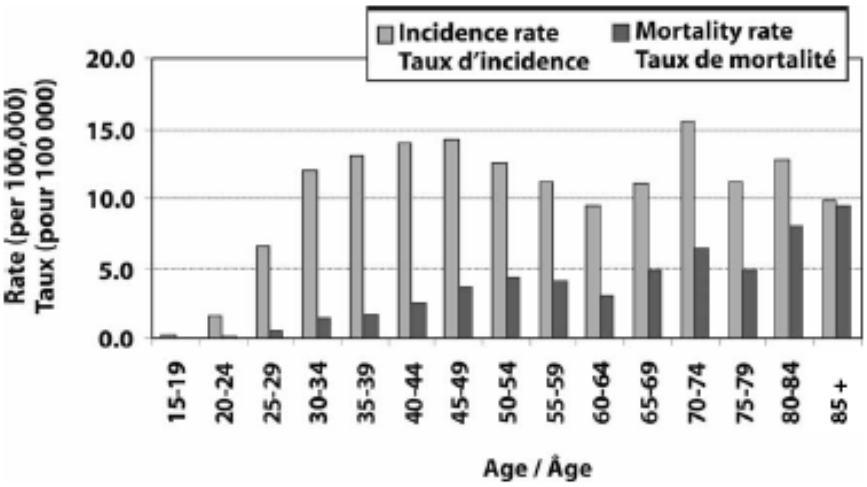


Source: *World Health Organization (2006) Comprehensive cervical cancer control: A guide to essential practice. ISBN 978 92 4 154700 0*

In 2006, according to the Health Agency of Canada, estimated new cases and deaths for cervical cancer in Canada are 1,350 and 300 respectively. Although cervical cancer incidence rates have decreased from 15.4 per 100,000 in 1977 to an estimated 7.5 per 100,000 in 2006, it remains the 11th most common cancer diagnosis in Canadian women and the 13th most common cancer-related cause of death [3]

The following figure illustrates cervical cancer incidence and mortality in Canadian society. It can be seen that incidence of cervical cancer is highest in women of 30-40 years of age, while mortality is much higher in older ages [4].

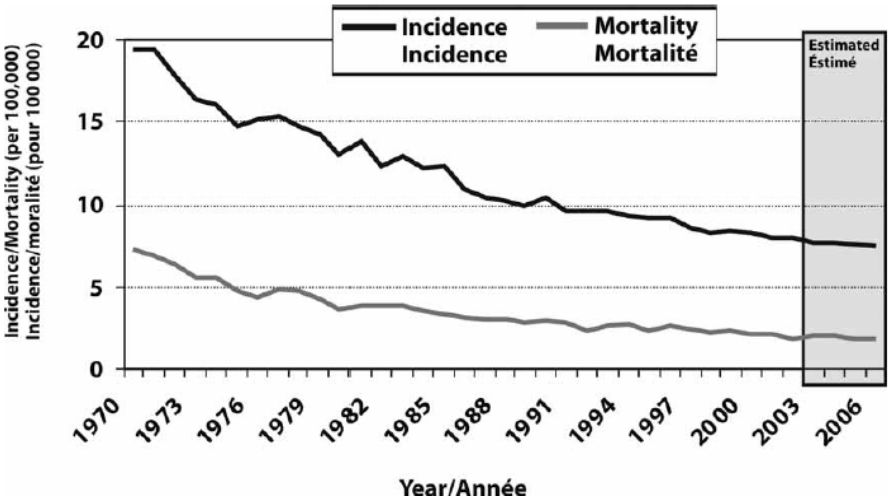
Graph 3 - *Cervical cancer incidence and mortality rates by age groups in Canada, 2003. From this graph it can be seen that mortality rates are highest in older age groups, while incidence rates are highest among young adults to adults.*



Source: *Public Health Agency of Canada. An Advisory Committee statement: National Advisory Committee on Immunization- Statement on human papillomavirus vaccine. Canada communicable disease report 2007; 33,1-32.*

Significantly declining rates of invasive cervical cancer (-2.0% incidence and -3.2 % mortality) likely reflects the impact of early detection and treatment of earlier detected cancers and pre-malignant lesions as a result of Pap smear screening [3]

Graph 4 *- Age-standardized cervical cancer incidence and mortality in Canada 1975-2006. From this graph it can be seen that both incidence and mortality have decreased in recent years due to medical advances in screening techniques.*



Source*: Public Health Agency of Canada. An Advisory Committee statement: National Advisory Committee on Immunization- Statement on human papillomavirus vaccine. Canada communicable disease report 2007; 33,1-32.*

Factors that influence the extent of survival rates in various populations are relative to proportions of patients with advanced versus early-stage disease; age distribution of the cohort of patients; access to surgery, radiation therapy and chemotherapy. These three factors are strongly correlated with socioeconomic status. Patients of lower economic means will have their diagnosis delayed, which may lead to more advanced disease at the time of treatment and consequently to poorer survival [1]. This can be best seen in North American Aboriginal, black and Hispanic populations, where cervical cancer accounts for nearly 15% of all cancers among women [4].

3.2 Pathogenesis

Cervical cancer is a malignancy of the cells lining the surface of the cervix. Infection with carcinogenic HPV types may lead to low-grade or high-grade intraepithelial lesions. High-grade lesions may progress to cervical carcinoma if not treated. HPV 16 accounts

for approximately 50% to 60% of invasive squamous cell carcinoma worldwide, and HPV 18 accounts for 60-75%. For adenocarcinoma, global evaluations have shown that HPV 16 is responsible for 40% of the cases, although HPV 18 is more commonly detected (about 30%) than in squamous cell carcinomas [2]. Together these two strains contribute to 70% of cervical cancer[4]. Most HPV infections are transient and resolve or become undetectable in couple of years. sometimes causing mild cytopathologic changes, including atypical squamous cells (ASC), low-grade squamous intraepithelial lesions (LSIL), and histopathologic cervical intraepithelial neoplasia Grade 1 (CIN1) changes. Bethesda classification system has been used to classify different stages of cervical lesions, and the following table gives further details, as well as corresponding CIN terms.

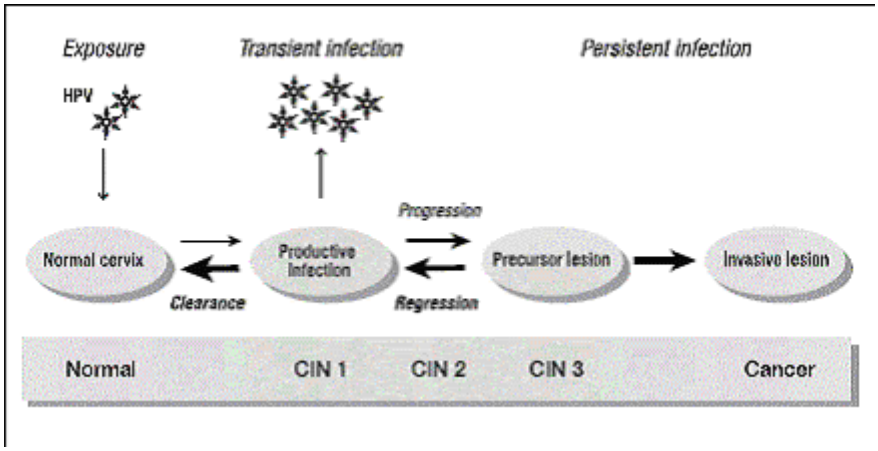
Table 2- *The Bethesda and CIN classication system for cervical squamous cell dysplasia.*

Betheda System 1999	Betheda System 1991	CIN System	Interpretation
Negative for intraepithelial lesions or malignancy	Within normal limits	Normal	No abnormal cells
ASC-H (atypical squamous cells of undertermined signifance)	ASCUS (atypical squamous cells of undetermined signifance)		Squamous cells with abnormalities greater than those attributed to reactive changes but that do not meet the criteria for a squamous intraepithelial lesions.
ASC-H (atypical squamous cells cannot exclude HSIL)	LSIL (low-grade squamous intraepithelial lesions)	CIN 1	Mildly abnormal cells; changes are almost always due to HPV
LSIL (low-graded squamous intraepithelial lesions)	HSIL (high-grade squamous intraepithelial lesions)	CIN 2/3	Moderately to severely abnormal squamous cells
Carcinoma	Carcinoma	Invasive squamous cell carcinoma. Invasive glandular cell carcinoma (adenocarcinoma)	The possibility of cancer is high enough to warrant immediate evaluation but does not mean that the patient definitely has cancer.

Source: *Burd E.M.. Human papillomavirus and cervical cancer. Clinical Microbiology Reviews 2003; 16 (1) 1-17.*

Women with persistent carcinogenic HPV infections are at the greatest risk of developing pre-cancerous lesions and then cancer. However, not all persistent infections progress to pre-cancerous (high-grade) lesions, and not all high-grade lesions develop into cancer. Approximately 75% of low grade lesions in adults and 90% of low-grade lesions in adolescents resolve without treatment [2,7]. The following picture shows a schematic illustration of progression of HPV infection to cervical cancer.

Picture 4- *Natural history of cervical cancer. Exposure of the cervix to human papillomavirus may cause a productive infection (CIN 1). This results in transient infection that can progresses to a precursor lesion (CIN 3) , but in most cases it regresses. In case of persistent infection, CIN 3 can further proliferate into an invasive lesion leading to cancer.*



Source: *World Health Organization (2006) Comprehensive cervical cancer control: A guide to essential practice. ISBN 978 92 4 154700 0*

In the oncogenic process, the viral genome incorporates itself into the host cell genome and develops a persistent infection. In the case of cervical dysplasia or cancer development, the immunity of mucosa is altered, with a decreased ability of the T cell helpers (Th1) to clear the HPV [4]. HPV E6 and HPV E7 proteins disrupt the host cell regulatory machinery, thereby allowing infected cells to replicate. In the case of

persistent HPV infection, these proteins disallow consistent repair or elimination of chromosomes with DNA damage [2]. The cancerous cellular changes are most likely to occur in the region of high cell turnover, termed transformation zone, which lies in between squamous and glandular mucus-secreting cells [4].

Cervical cancer starts as asymptomatic pre-cancerous lesion and develops gradually over many years. The intraepithelial lesions are limited to the cervical epithelium, and as invasion occurs the neoplastic cells penetrate the underlying membrane with potential for widespread dissemination. Depending on their severity, lesions can resolve spontaneously or can progress to cancer. Mild dysplastic changes evolve into severe dysplastic changes and ultimately into *in situ* carcinoma and, if untreated, invasive squamous cell carcinoma. Most of the immunologically competent women who are infected with oncogenic HPV will clear the infection without its progression to cervical cancer [4].

3.3 Risk Factors

As mentioned above, human papillomavirus has been found in 99.7% of cervical squamous cell cancer cases worldwide and is the main risk factor for the development of cervical cancer [5]. Other important factors that directly and indirectly influence development of cervical cancer include number of sexual partners, age at first sexual intercourse and sexual behaviour of the woman's male partners. Higher the number of sexual partners a woman has in her lifetime as well as her partner and younger the age of onset of sexual activity all increase the risk. As well, tobacco smoking is a risk factor for cervical cancer due to direct carcinogenic action of cigarette smoking on the cervix. It may contribute to persistence of HPV or to malignant transformation. Cigarette smoking is the most important risk factor independent of HPV infection for higher grades of cervical disease, while it shows little or no relationship to low grades of cervical disease [1,5,12].

There is also a risk of cervical cancer associated with long-term use (12 years or more) of oral contraceptives. This association is somewhat greater for adenocarcinomas than for

squamous cell carcinomas [1]. The upstream regulatory region of HPV contains sequences similar to the glucocorticoid responsive elements that are inducible by steroid hormones such as progesterone and dexamethasone. However it is difficult to evaluate this risk factor due to high association of oral contraceptives and sexual activity [13]. Genetic heritability could affect many factors contributing to the development of cervical cancer, including susceptibility to HPV infection, ability to clear HPV infection, and time to development of disease [5].

3.4 Prevention

Primary prevention includes prevention of HPV infection and cofactors known to increase the risk of cervical cancer. Education and awareness focused at reducing high-risk sexual behaviors, promoting the use of condoms, as well as discouraging tobacco use, are one of the government strategies aimed at eliminating this disease [13]. The most important factor is regular screening by Pap smears and focus on development and introduction of an effective and affordable HPV vaccination programs [12]. Details regarding prevention of development of cervical cancer and genital warts with HPV quadrivalent vaccine will be the focus of the following chapter, as well as the rest of this bibliographical research work.

3.5 Detection

Early detection involves organized screening programs. The usual 10 to 20 year natural history of progression from mild dysplasia to carcinoma makes cervical cancer a relatively easily preventable disease and provides the rationale for screening. Cytology-based screening and treatment programs have reduced cervical cancer incidence and mortality by as much as 80% in Canada, the USA and some Scandinavian countries, and by 50–60% in other European countries. [7]

Several tests can be used in screening for cervical cancer, while the Pap smear is the only one that has been used in large populations and that has been shown effective in reducing cervical cancer incidence and mortality. Other tests include liquid-based cytology, HPV DNA test and visual inspection tests with acetic acid (VIA) and Lugol's iodine (VILI).

The Pap test involves scraping cervical cells with a spatula, placing them on a slide and examining it under a microscope. This test can identify both pre-cancerous lesions, which can then be treated so that cancer does not develop, and cancers at an early pre-symptomatic stage when treatment is most effective [3].

In liquid based cytology, instead of smearing cervical cells on a slide, the examiner transfers the specimen from a brush to a preservative solution. The specimen is sent to a laboratory where the slide is prepared and observed. This method is more expensive and requires more highly trained personnel than Pap smear procedure. However liquid based cytology leads to less false-negative results, has shorter interpretation time and can detect HPV DNA [7].

HPV DNA-based tests are based on sample of cells collected from the cervix or vagina, and placed in a small container with a preservative solution, from which the smear is prepared. This test require sophisticated and expensive laboratory equipment, therefore is not a preferred method of detection.

Two visual methods currently available include visual inspection with acetic acid (VIA) and visual inspection with Lugol's iodine (VILI). Abnormalities are identified by inspection of the cervix after application of dilute acetic acid or Lugol's iodine. When these chemicals are applied to abnormal cervical tissue, it temporarily turns white allowing the examiner to make an immediate assessment of a positive (abnormal) or negative (normal) result. These two methods are still under clinical trials and will require some time before they are implemented in the large population scale [7].

3.6 Diagnosis and Treatment

Diagnosis and treatment strategies include follow-up of patients who are positive on screening, in order to make appropriate diagnosis and disease management plan. It also involves treatment of pre-cancer, prevention of the development of cancer; as well as treatment of invasive cancer, including surgery, radiotherapy and chemotherapy [7].

The standard method for diagnosis of cervical pre-cancerous lesions is histo-pathological examination of tissue obtained through biopsy guided by colposcopy. This procedure involves the examination of the cervix, vagina and vulva with a colposcope, which provides illumination and magnification, allowing the cellular patterns in the epithelial layer and surrounding blood vessels to be examined. Application of dilute acetic acid highlights abnormal areas, which can then be biopsied. Further diagnostic procedures are loop electrical excision procedure (LEEP) and conization, in which the inner lining of the cervix is removed to be examined pathologically. These are carried out if the biopsy confirms severe cervical intraepithelial neoplasia [7].

4. EXTERNAL GENITAL LESIONS

External genital warts are the most common recognized clinical manifestation of genital HPV infection. They are visible cauliflower-like warts that occur in the perigenital and perianal regions. The main cause of their occurrence is due to non-oncogenic human papillomavirus types 6 and 11, which are responsible for 97% of all genital warts [9,10,11]. They are usually self-limited lesions in immuno-competent individuals, resolving typically in 12 to 24 months [4]

The prevalence of HPV infection varies, but it is estimated that 1% of the adult population have symptomatic external genital warts [10]. Approximately 10% of men and women will develop anogenital warts at some point in their lives [2]. In United States its is approximated that 5 to 10 million of new cases are diagnosed each year [9] Most genital warts occur during the first few years after the onset of sexual activity and are transient.

Currently there are no published population-based studies on the disease incidence of anogenital warts in most countries. However, when looking at data provided from family practice settings in Canada, in a sample of women 15 to 49 years of age, 1.1% were reported to have genital warts. Due to the lack of published data prevalence estimates are largely based on epidemiologic studies and on surveillance activities in developed countries. In England, anogenital warts are the most common viral sexually transmitted infection diagnosed at clinics, accounting for 11% of all diagnoses. According to US statistics in the year 2004, the highest prevalence of genital warts was in the 20 to 24 year old age group among males, and 16 to 19 year old females [4].

Primary diagnosis is done by direct visual inspection with bright light and magnification. Treatments are either self treatment or provider treatment. Provider applied treatments include surgical treatments such as electrosurgery, surgical excision, cryotherapy, and laser surgery. Nonsurgical provider-prescribed and -applied therapies include

podophyllin resin, IFN, and bi- and tri-chloroacetic acid. Patient- applied nonsurgical treatments include podophyllotoxin, imiquimod , and 5-fluorouracil cream. [10]

Reoccurrence problems are common and no single treatment is preferred. The need for treatment is based on patient needs, such as less painful treatment, less visits to the doctor and less cost. Self-applied therapies are less expensive but treatment may take longer time [9].

Use of condoms and abstinence are common preventive measures. However the HPV vaccine containing HPV type 16 and 18 VLP plays a major role in preventing development of external genital warts.

5. HPV VACCINE

Gardasil is a non-infectious recombinant, quadrivalent vaccine prepared from the highly purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, and 18. The L1 proteins are produced by separate fermentations in recombinant *Saccharomyces cerevisiae* and self-assembled into VLPs. The quadrivalent HPV VLP vaccine is a sterile liquid suspension that is prepared by combining the adsorbed VLPs of each HPV type and additional amounts of the aluminum-containing adjuvant and the final purification buffer.

The quadrivalent HPV vaccine has been given two different names Gardasil and Silgard which differ upon marketing companies. Silgard is marketed by Sanofi Pasteur MSD (SPMSD), a joint venture between Sanofi Pasteur and Merck & Co., Inc, in 19 European countries including 15 in the EU. While in the remaining Central and Eastern European countries, GARDASIL is marketed by Merck Sharp & Dohme as either GARDASIL or SILGARD(R).

5.1 Mechanism of Action

Currently, there are no animal models for human papillomavirus infection. Designs of animal models vaccination with L1 Virus-like Particles (VLPs) derived from species-specific papillomaviruses protected against infectious disease. The quadrivalent HPV vaccine was developed based on animal data that suggest that a systemic neutralizing anti-HPV response by vaccination with type-specific HPV L1 VLPs result in protective immunity against type-specific HPV infection and disease.

The HPV major capsid protein, L1, can spontaneously self-assemble into virus-like particles (VLPs) that resemble authentic HPV virions. Gardasil/Silgard contains recombinant VLPs assembled from the L1 proteins of HPVs 6, 11, 16 and 18. Specifically, the vaccine elicits cell-mediated responses as detected by in vitro stimulation of Peripheral Blood Mononuclear Cells (PBMCs), Th1 and Th2 cytokines

and immunoglobulin subclasses. The exact immune response mechanism is not know. However, it is believed that the vaccine provides protection by inducing type-specific antibodies that interfere with transmission by binding to and neutralizing HPV prior to its entry into basal cells.

5.2 Dosage and Administration

Gardasil should be administered intramuscularly as 3 separate 0.5-mL doses with the first dose at elected date, second dose at 2 months after the first dose and the final dose 6 months after the first dose.

The vaccine should be administered intramuscularly in the deltoid region of the upper arm or in the higher area of the thigh. It must not be injected intravascularly. Subcutaneous and intradermal administration have not been studied, and therefore are not recommended. The vaccine is supplied as a carton of one or ten 0.5 ml single dose vials.

II. QUADRIVALENT HPV VACCINE (GARDASIL/SILGARD) CLINICAL TRIALS

1. INTRODUCTION

Clinical studies were designed to provide satisfactory evidence of quadrivalent HPV vaccine clinical effectiveness in order to support its licensing. It included approximately 21,514 subjects from all over the world, where 11,813 were vaccinated and 9,701 were given a placebo [17,18].

Recently developed quadrivalent HPV vaccine Gardasil manufactured by Merck co. has been a focus in primary prevention of HPV infections. It has been implemented in national plan by several countries. The remaining focus of this work will be regarding this new method of preventive health care and the potential benefits of implementing national vaccination programs.

1.2 Aim of Clinical Studies

PHASE I/IIa STUDIES

In general, phase I trials are initial studies to determine the metabolism and pharmacological actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness. Phase II trials are controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication and to determine the common short-term side effects and risks [26].

Gardasil phase I/IIa studies assessed immunogenicity and safety of monovalent vaccine variants.

- Protocol 001 evaluated HPV 11 LI VPL vaccine
- Protocols 002, 004 and 005 evaluated HPV 16 LI VPL vaccine
- Protocol 006 evaluated HPV 18 LI VPL vaccine.

PHASE IIb/III STUDIES

Phase III trials are controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained. They are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide and adequate basis for physician labeling [26].

Phase IIb/III trials dealt with quadrivalent HPV vaccine program, which was divided into two sets of studies; the first set consisted of efficacy studies, while the second set were studies to bridge efficacy, immunogenicity and safety in 16 to 23 year old females to its younger age cohorts [17,18].

Immunogenicity of quadrivalent HPV vaccine was evaluated in the following studies and involved 12,345 participants

- Protocol 007- Dose Selection Study
- Protocol 011- Concomitant Hepatitis B vaccine
- Protocol 012- Monovalent HPV 16 bridging
- Protocol 015V1- Consistency lots

Four randomized placebo controlled clinical trials assessed efficacy of the vaccine and included total of 20,541 participants aged 16 to 26 years. Most of them were HPV naïve, but were at risk of HPV infection [17,18]. In short these studies were;

- Protocol 005- phase II study, evaluated HPV 16 component
- Protocol 007- phase II study, evaluated the quadrivalent HPV (6,11,16,18 types) LI VPL vaccine
- Protocol 013- phase III study, FUTURE I (Female United to Unilaterally Reduce Endo/Ectocervical Disease), evaluated quadrivalent vaccine in prevention of HPV 6/11/16/18 related CIN/ external genital lesions (EGLs)
- Protocol 015- phase III study, FUTURE II, evaluated quadrivalent vaccine in prevention of HPV 16 or HPV 18 related CIN 2/3 or AIS (Cervical Adenocarinoma in situ)

Safety of both monovalent (4,228) and quadrivalent (11,813) vaccines was evaluated in total of 16,041 subjects. All studies were placebo controlled, with 9,701 participants receiving placebo [17,18].

Pharmacokinetics

Not performed in accordance with the note for guidance on clinical evaluation of new vaccines.

Pharmacodynamics

This section evaluated data on systemic immune response to vaccination.

Phase I/IIa studies evaluated immunogenicity of monovoalent HPV vaccines and it included protocols 001,002,006,004,005.

Phase IIb/III studies evaluated immunogenicity of quadrivalent HPV vaccines, and it included protocols 007, 012, 013 and 015.

Three methods were used to measure the immunogenicity of the HPV vaccines. They included a competitive radio-immunoassay (cRIA),a competitive Luminex-based immunoassay (cLIA) and a xenograft based HPV 11 neutralization (NT) assay. The immune response to each vaccine HPV type was measured separately [17,18].

Primary study population consisted of per-protocol immunogenicity (PPI) population defined as subjects who were seronegative and PCR negative to the relevant HPV type(s) at Day 1, remained HPV PCR negative through 1 month post dose 3, received all 3 vaccinations within pre-specified time intervals, and no deviation from the study protocol.

The primary aim of immunogenicity studies was to

- Evaluate vaccine-induced serum anti-HPV responses during the vaccination regimen, 4 weeks following the completion, as well as persistence of antibody response after 3.5 years
- Define impact of base-line covariates (e.g. age, gender, ethnicity) and deviations from vaccination regimen at 4 weeks post last dose (dose 3)
- To bridge the efficacy data obtained in female subjects aged 16 to 26 years to subjects 10 to 15 years of age at enrolment, by demonstrating that the last dose anti-HPV responses in the younger age group are non-inferior to those observed in the older group
- For HPV 11 to demonstrate that immune responses are virus neutralizing
- To establish that vaccine-induced responses are comparable or superior to immune responses to natural infection
- To establish that the HPV vaccine can generate memory responses in subjects seropositive for one or more HPV types at start of study
- To investigate potential immune correlates of vaccine efficacy

Primary immunological endpoints were:

- Geometric mean titres (GMTs) of anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV at month 7
- Proportion of subjects who sero-converted to each of the four antigens 4 weeks after the third dose.

The minimum anti-HPV levels associated with protection from acquisition of HPV is not currently know; therefore the cut-off value of validated assays was used as a surrogate for seropositive level [17,18]. The cLIA cutoffs for seropositivity were as follows:

- ≥20 mMU/ml for HPV 6 and 16
- ≥16 mMU/ml for HPV 11
- ≥24 mMU/ml for HPV 18.

2. MONOVALENT HPV VACCINE STUDIES

Initial phase I/IIa studies (protocols 001, 002, 004 & 006) aimed to evaluate immunogenicity of monovalent vaccine precursors. These studies included 3,160 females aged 16 to 26 years. Of those, 1,842 received a vaccine and 1,318 received a placebo. All studies were randomized, double blind and placebo-controlled and all vaccine candidates were given in a 3-dose schedule (0, 2, 6 months) [17,18].

2.1 Protocol 001: The Safety,Tolerability and Immunogenicity of HPV 11 Virus-Like Particle (VLP) Vaccine in College Women

2.1.1 Objective

This trial was conducted in order to determine the safety and immunogenicity of four dose formulations of monovalent HPV 11 L1 VLP vaccine (administered at 0, 2 and 6 months) in women 18-25 years of age.

Primary immunogenicity endpoint was the percentage of subjects achieving anti-HPV 11 serum RIA levels $\geq$ 200 mMU/mL at 4 weeks post dose 3 with 95% confidence interval (CI).

2.1.2 Method Design

Phase I, randomized, double-blind, sequential dose-escalating placebo controlled trial .

Table 3- *Treatment plan for protocol 001*.

		Sample size		
Group	**Dosage (mcg)**	**HPV**	**Placebo**	**Total**
A	10	28	7	35
B	20	28	7	35
C	50	28	7	35
D	100	28	7	35
Total				140

Source*: K.H. Fife, C.M. Wheeler, L.A. Koutsky, E. Barr, D.R. Brown and M.A. Schiff et al., Dose-ranging studies of the safety and immunogenicity of human papillomavirus Type 11 and Type 16 virus-like particle candidate vaccines in young healthy women, Vaccine 22 (2004), pp. 2943–2952*

Vaccine products used for research lot preparations were;

- 10 mcg/0.5 mL HPV 11 L1 VLP vaccine
- 20 mcg/0.5 mL HPV 11 L1 VLP vaccine
- 50 mcg/0.5 mL HPV 11 L1 VLP vaccine
- 100 mcg/0.5 mL HPV 11 L1 VLP vaccine
- Placebo - V501 HSS001 A001 (225 mcg aluminum as amorphous aluminum hydroxide sulfate or AAHS)

2.1.3 Participants

The participants were healthy females 18-25 years of age (mean 20.6 years) and seronegative for anti-HPV 11. Ethnic distribution was Caucasian (82.1%), Hispanic (9.3%), Black (4.3%), and Asian (3.6%). The subjects could not have a history of evidence of HPV related disease. Subjects had to have a negative pregnancy test on the day of vaccination in order to receive study material.

2.1.4 Results

Participants

Out of 140 participants participating in the study, 116 have completed it. None of the participants discontinued from the study due to adverse event, most common reasons were lost to follow up, refusal to participate, or became pregnant.

Immunogenicity Results

Primary Immunogenicity Results

The monovalent HPV 11 vaccine induced anti-HPV 11 antibody response at all doses tested. Similar results were seen for this analysis with the HPV 11 naïve with serology population. Also neutralization of HPV 11 was demonstrated at all tested doses.

The following table illustrates proportion of subjects with anti-HPV 11 $\geq$ 200 mMU/mL and GMTs at week 4 post-dose 3 (Per Protocol Population) and neutralization response.

Table 4- *Percentage of subjects with anti HPV 11 GMT levels greater than 200 mMU/ml at different doses of HPV 11 L1 vaccine.*

Treatment Group	N	% of subjects with anti-HPV 11 GMT > 200 mMU/ml (95% CI)	GMT (mMU/mL)	% of subjects with HPV 11 Neutralization at Month 7 (95% CI)
Placebo	11	0% (0.0,28.5)	<10.0	0% (0.05,28.5)
HPV 11 L1 VLP **10 mcg**	4	75% (19.4,99.4)	594.7	100% (39.8,100.0)
HPV 11 L1 VLP **20 mcg**	15	86.7% (59.5, 98.3)	517.5	73.3% (44.9,92.2)
HPV 11 L1 VLP **50 mcg**	13	92.3% (64.0,99.8)	538.1	84.6% (54.6, 98.1)
HPV 11 L1 VLP **100 mcg**	17	100% (80.5,100.0)	1222.5	100% (80.5,100)

Source*: K.H. Fife, C.M. Wheeler, L.A. Koutsky, E. Barr, D.R. Brown and M.A. Schiff et al., Dose-ranging studies of the safety and immunogenicity of human papillomavirus Type 11 and Type 16 virus-like particle candidate vaccines in young healthy women, Vaccine 22 (2004), pp. 2943–2952*

Other Secondary Immunogenicity Results

- There was evidence of persistence of anti- HPV 11 antibodies at Month 36
- Administration of a fourth dose did not appear to produce meaningful increases in the antibody levels at Month 36.
- There was a suggestion of a dose response, since there was a significant difference between placebo and the 10 mcg dose in percentage of subjects with an anti-HPV 11 antibody level $\geq$ 200 mMU/mL.

Safety Evaluation

- There was a higher percentage of subjects reporting an adverse event (AE) after the first dose as compared to the second and third doses.
- Most of the injection site AEs were mild to moderate, and most common systemic AEs was headache
- The overall incidences of systemic AEs were higher in the 50 and 100 mcg doses.

2.1.5 Conclusion

The 20-, 50-, and 100-mcg dose levels of HPV 11 L1 VLP vaccine appear immunogenic. Administration of a fourth dose does not produce meaningful increases in antibody levels at Month 36 as compared to the 3 dose regimen. No safety issues were identified from this Phase I trial.

2.2 Protocol 002: Safety/Tolerability and Immunogenicity of HPV 16 Virus-Like Particle (VLP) Vaccine in College Women

2.2.1 Objective

To determine the safety and immunogenicity of three dose formulations of monovalent HPV 16 L1 VLP vaccine in young women 18-25 years of age [19].

2.2.2 Method Design

This was a phase I, randomized, double blind, sequential dose-escalating, placebo controlled trial. Method design is summarized in the following table.

Table 5- *Treatment plan of Protocol 002.*

		Sample size		
Group	**Dosage (mcg)**	**HPV 16 L1**	**Placebo**	**Total**
A	10/40	13	4	17
B	40	45	15	60
C	80	24	8	32
Total				109

Source: *K.H. Fife, C.M. Wheeler, L.A. Koutsky, E. Barr, D.R. Brown and M.A. Schiff et al., Dose-ranging studies of the safety and immunogenicity of human papillomavirus Type 11 and Type 16 virus-like particle candidate vaccines in young healthy women, Vaccine 22 (2004), pp. 2943–2952*

Vaccine products used for research lot preparations were;

- 10 mcg/0.5 mL HPV 16 L1 VLP vaccine
- 40 mcg/0.5 mL HPV 16 L1 VLP vaccine
- 80 mcg/0.5 mL HPV 16 L1 VLP vaccine
- Placebo - V501 HSS002 A002 (225 mcg aluminum as amorphous aluminum hydroxide sulfate or AAHS)

Safety Endpoints

Primary safety endpoints were incidences of AEs that were vaccine related and severe injection site AEs.

Efficacy Endpoints

Efficacy was not an endpoint, but exploratory endpoints included the rate of incident HPV 16 infection, the rate of incident HPV 6, 11, and 18 infections, the incidence of HPV related disease, and the association between PCR responses and Pap test results

2.2.3 **Participants**

Participants were healthy 18-25 year old women who were naïve for HPV 16 infection at baseline (women enrolled were to be HPV 16 seronegative and PCR negative at screening), had 0-5 lifetime sexual partners, and had no history of abnormal Pap test [19].

The following populations were defined

- **Per Protocol Population (PPP):** naïve for HPV 16 through Month 7, received all 3 doses of vaccine, and serology within day ranges and after third dose.
- **All HPV 16 naïve subjects with serology data:** Naïve for HPV 16 through month 7 had month 7 serology results, and includes violators.

2.2.4 **Results**

Out of 109 participants, 103 have completed the vaccination regime (up to month 7) and the mean age was 20.3 years old. The following table summarizes immunogenicity of percentage of subjects achieving anti HPV 16 RIA > 20 mMU/ml and GMTs with 95% CI ,PPP at month 7.

Table 6- *Percentage of subjects treated with various doses HPV 16 L1 VLP that had serum levels greater than 20 mMU/ml.*

Treatment Group	n	% of Subjects with Serum HPV 16 RIA >20 mMU/ml (95% CI)	GMT mMU/ml (95% CI)
Placebo	23	0% (0.0,14.8)	< 6.0
HPV 16 L1 VLP **10/40mcg**	8	100% (63.1,100.0)	447.9 (185.3,1082.9)
HPV 16 L1 VLP **40mcg**	35	100% (90.0,100.0)	823.6 (630.9,1075.2)
HPV 16 L1 VLP **80 mcg**	20	100% (83.2,100.0)	732.2 (420.7,1274.6)

***Source**: K.H. Fife, C.M. Wheeler, L.A. Koutsky, E. Barr, D.R. Brown and M.A. Schiff et al., Dose-ranging studies of the safety and immunogenicity of human papillomavirus Type 11 and Type 16 virus-like particle candidate vaccines in young healthy women, Vaccine 22 (2004), pp. 2943–2952*

The secondary immunogenicity analysis showed that all dose formulation elicited an immune response to anti-HPV 16, and GMT levels persisted through to month 36 for all doses. It is important to note that two subjects naïve to HPV 16 developed HPV type 16 infection; both were in placebo group.

Safety evaluation

- There was no discernible difference in safety profile after doses 1, 2 and 3.
- In all treatment groups, the majority of adverse events were reported as being mild or moderate, and these rates were generally comparable among treatment groups.
- The most common Injection Site AE was pain/tenderness/soreness
- The most common Systemic Clinical AE was headache

The following table summarizes incidence of all adverse events AEs among different treatment groups.

Table 7- *Summary of adverse effects according to different test groups in protocol 002.*

Treatment Group	Injection Site AE incidence	Systemic Clinical AE incidence
Placebo	63.0% (17/27)	96.3% (26/27)
10/40 mcg dose	46.2% (6/13)	92.3% (12/13)
40 mcg dose	77.8% (35/45)	82.2% (37/45)
80 mcg dose	70.8% (17/24)	91.7% (22/24)

Source: *K.H. Fife, C.M. Wheeler, L.A. Koutsky, E. Barr, D.R. Brown and M.A. Schiff et al., Dose-ranging studies of the safety and immunogenicity of human papillomavirus Type 11 and Type 16 virus-like particle candidate vaccines in young healthy women, Vaccine 22 (2004), pp. 2943–2952*

2.2.5 Conclusion

It is important to note that originally subjects were to be randomized 3:1 to panels of sequentially higher doses HPV 16 L1 VLP vaccine or placebo. Early in the study 10mcg dose showed decreased immunogenicity in mice. Therefore, subjects randomized for 10 mcg dose were subsequently given 40 mcg dose.

The 40 mcg and 80 mcg doses of the HPV 16 L1 VLP vaccine appear immunogenic. The immune responses to all doses of the vaccine lasted for at least 36 months. No safety concerns were noted [19].

2.3 Protocol 004: Immunogenicity Study of Pilot Manufacturing Material of HPV 16 VLP Vaccine in 18-25 year old Women

2.3.1 Objective

This study aimed to determine the safety of 3 doses (Month 0, 2, and 6) of pilot manufacturing material of HPV 16 VLP vaccine in subjects who are either HPV 16 seronegative or seropositive prior to vaccination. It also assessed the antibody response levels for 4 doses of the vaccine (10, 20, 40 and 80 mcg) [19].

2.3.2 Method Design

Phase IIa, randomized, double blind, placebo controlled study. Participants were followed for 14 days after each vaccination (last dose at Month 6), and evaluated persistence of anti-HPV antibody through Month 24 [19]. Treatment plan is summarized in the table below.

Table 8- *Method design of protocol 004 according different dosage levels, showing sample size and dosage schedule.*

Dosage Level (Vaccine/Placebo)	Sample Size	Dosage schedule
Placebo	52	0, 2, 6 months
HPV 16 L1 VLP **10** mcg/0.5 mL	112	0, 2, 6 months
HPV 16 L1 VLP **20** mcg/0.5 mL	105	0, 2, 6 months
HPV 16 L1 VLP **40** mcg/0.5 mL	104	0, 2, 6 months
HPV 16 L1 VLP **80** mcg/0.5 mL	107	0, 2, 6 months
Total	480	0, 2, 6 months

Source: *K.H. Fife, C.M. Wheeler, L.A. Koutsky, E. Barr, D.R. Brown and M.A. Schiff et al., Dose-ranging studies of the safety and immunogenicity of human papillomavirus Type 11 and Type 16 virus-like particle candidate vaccines in young healthy women, Vaccine 22 (2004), pp. 2943–2952*

The following pilot manufacturing vaccine materials used;

- 10 mcg/0.5 mL HPV 16 L1 VLP vaccine
- 20 mcg/0.5 mL HPV 16 L1 VLP vaccine
- 40 mcg/0.5 mL HPV 16 L1 VLP vaccine
- 80 mcg/0.5 mL HPV 16 L1 VLP vaccine
- Placebo – PV501 HSS009A001 (225 mcg aluminum as amorphous aluminum hydroxide

Primary variable for immunogenicity

The proportion of subjects achieving anti-HPV 16 serum cRIA levels >20mMU/ml 4 weeks post dose 3 (month 7)

Secondary immunogenicity parameters

These included anti HPV 16 serum cRIA GMTs at 4 weeks post dose 3.

Primary variables for safety

These included the occurrence of any severe local injection site reactions and the incidence of any serious vaccine related AEs.

2.3.3 Participants

Included healthy females 16-23 years of age. These subjects were not screened for HPV 16 disease prior to enrollment.

The following populations were defined;

- **The per-protocol population –** it was used in the primary analysis, and included subjects who received 3 doses of vaccine and were not protocol violators, and had serology at correct time points and after the third dose of vaccine. They were seronegative at baseline [19].
- **HPV 16-Naïve Subjects With Serology Data:** Includes all subjects who were anti-HPV 16 cRIA seronegative at baseline and were free of detectable HPV 16 DNA (PCR) at Day 0 through Month 7, but could be protocol violators [19].

2.3.4 Results

Out of 480 initially enrolled participants, 384 completed the vaccination phase. The majority of those who dropped out, did so because of refusal to participate.

The following percentages were noted among participants; 1.3% had abnormal Pap smear; 0.4% had history of genital warts; 0.1% history of cervicovaginal infections.

All of the dose levels have shown to induce acceptable immune responses (cRIA levels of anti HPV 16 GMTs >20 mMU/ml) at week 4, following dose 3 (month 7) [19]. The following table summarizes these results.

Table 9- *Percentage of subjects treated with various doses HPV 16 L1 VLP that had serum levels greater than 20 mMU/ml in protocol 004.*

Treatment Group	**n**	**% of Subjects with Serum HPV 16 RIA levels >20 mMU/ml (95% CI)**	**GMT Mmu/ml (95% CI)**
Placebo (N= 52)	24	0 % (0.0, 14.2)	<6.0
HPV 16 L1 VLP **10** mcg (N= 112)	52	98.1 % (89.7, 100.0)	981.6 (680.8, 1415.2)
HPV 16 L1 VLP **20** mcg (N= 112)	40	100 % (91.2, 100.0)	2045.2 (1444.6, 2895.4)
HPV 16 L1 VLP **40** mcg (N= 105)	46	100 % (92.3, 100.0)	1790.4 (1384.0, 2346.0)
HPV 16 L1 VLP **80** mcg (N= 104)	45	100 % (91.2, 100.0)	2109.0 (1584.3, 2807.4)

N= number vaccinated; n = number evaluated

Source: *K.H. Fife, C.M. Wheeler, L.A. Koutsky, E. Barr, D.R. Brown and M.A. Schiff et al., Dose-ranging studies of the safety and immunogenicity of human papillomavirus Type 11 and Type 16 virus-like particle candidate vaccines in young healthy women, Vaccine 22 (2004), pp. 2943–2952*

Immunological dose responses at months 12, 18 & 24 showed statistical difference from placebo and 10mcg dose. It was true for PPP and all HPV 16 naïve with serology populations.

Safety Evaluation

- Majority of adverse events (AE) were graded mild to moderate in severity, and were comparable across dose groups.
- One placebo participant withdrew from program due to AE, headache.
- There was no indication of relation between dose and severe AEs.
- In 10mcg and 40 mcg groups, the percentage of baseline seropositive subjects reporting severe AEs were approximately twice higher than the percentage of baseline seronegative subjects. (31%,19.2% vs.14.5, 7.7%)
- Injection site AEs were mild to moderate in severity and mostly included pain, tenderness and soreness.
- Systemic AEs were mild to moderate in severity and it included mostly headache. However incidence of fever in the first 14 days was higher in vaccine group than in the placebo group (6.7% vs. 2%)
- Impact of vaccination on pregnancy group- There were 2 pregnancies in placebo group with delivery of healthy babies. There were 17 pregnancies in vaccine groups- 2 miscarriages, 4 termination of pregnancies, 8 healthy infants, 1 infant with congenital anomaly.

2.3.5 Conclusion

This protocol showed that all HPV 16 L1 VLP active vaccine dose levels were immunogenic. Anti-HPV 16 serum cRIA responses decrease upon completion of the vaccination program; but, at 18 months Postdose 3, these levels were detectable in the majority of vaccines and anti-HPV 16 GMTs remained numerically higher than those in women who developed anti-HPV 16 responses to natural infection.

In baseline anti-HPV 16 seropositive subjects, anti-HPV 16 responses to the HPV 16 L1 VLP vaccine appear numerically higher than those in baseline seronegative subjects at Month 3, Month 7, and in month 24. There was no specific safety concern identified [19].

2.4 Protocol 006: A Study of the Safety/Tolerability and Immunogenicity of HPV 18 Virus Like Particle (VLP) Monovalent Vaccine in 16-23 year old Women

2.4.1 Objective

The aim of this study was to evaluate the safety and tolerability of three doses of the HPV 18 L1 VLP vaccine in women and to assess the immunogenicity of the vaccine in HPV 18 seronegative and PCR negative women. Secondary aim was to obtain safety experience with the vaccine in women who are positive for HPV 18 [22].

2.4.2 Methods Design

This study was phase II, double blind, placebo controlled trial. The treatment plan consisted of group A participants that received HPV 18 LI VLP 80mcg vaccine, and Group B that received placebo. Both were vaccinated at 0,2 & 6 months dosage schedule.

Primary variable of interest for immunogenicity

- It was the proportion of subjects achieving an anti-HPV 18 serum cRIA level $\geq$ 200 mMU/mL at month 7 [22]

Safety Parameters

- The primary variables were the occurrence of severe, local injection-site reactions and the incidence of any serious vaccine-related adverse experiences.
- The incidences of injection-site adverse experiences for first 14 days, or specific systemic adverse experiences within 14 days post-vaccination were tabulated for both treatment groups [22].

Efficacy Parameters

- This protocol was not designed as an efficacy study; but it was designed to collect specimens that could be used to evaluate vaccine efficacy [22].
- **Incident HPV 18 infection rates** – termed as detection of HPV 18 DNA by the type-specific HPV 18 PCR assay in cervicovaginal specimens obtained at Month 7 in women who were HPV 18 naïve at enrollment.
- **Clinical HPV disease**- termed as the development of new HPV-related Pap test abnormalities and CIN detected in biopsy specimens in subjects who had a negative Pap test at enrollment [22].

2.4.3 Participants

Forty healthy females aged 17-23 years old, who didn't have a history of prior Pap Test abnormalities participated in this study. Originally 27 were in vaccine and 13 in placebo group, but 25 in vaccine and 12 in placebo group completed the full regimen [22].

The following populations were defined:

- **Per-protocol population (PPP**) used in the primary analysis. It excluded protocol violators, subjects who were not HPV 18-naïve at enrollment, and subjects who acquired HPV 18 infection during the vaccination regimen.
- **The Population of All HPV 18-Naïve Subjects With Serology Data.** It includes all subjects who were anti-HPV 18 cRIA seronegative at Day 0 and were free of detectable HPV 18 DNA (PCR) at Day 0 and Month 7. This approach includes general protocol violators [22].

2.4.4 Results

Immunogenicity Results

Evidence showed that the HPV 18 L1 VLP vaccine induced acceptable immune response in the PPP. The following table summarizes immunogenicity of Anti-HPV 18 serum cRIA responses to the vaccine in initially seronegative participants for PPP at month 7.

Table 10- *Percentage of subjects having anti-HPV 18 serum cRIA greater than 200mMU/ml in each treatment group of protocol 006.*

Treatment Group	N	% of subjects with Anti-HPV 18 Serum cRIA >200 mMU/ml (95% CI)	GMT mMU/ml (95% CI)
Placebo	11	0 % (0, 28.5)	<13.0
HPV 18 L1 VLP 80 mcg	22	100 % (84.6,100)	1448.3 (1004,2089.4)

***Source**: K. Ault, Giuliano A., Edwards P et al., A phase I study to evaluate a human papillomavirus (HPV) type 18 L1 VLP vaccine. Vaccine 22 (2004) 3004-3007.*

It is important to note that subjects who were initially HPV 18 PCR negative at the beginning of the study, none became positive at month 7.

Safety Evaluation

- All subjects were followed for adverse events for 15 days after each vaccination.
- The proportions of subjects reporting a clinical adverse event were comparable between treatment groups and most of the AEs were mild in severity.
- The placebo group had a higher frequency of reports of severe adverse events 9.9% compared with 2.7% for the vaccine group.
- More subjects in the vaccine group reported an AE with a maximum intensity of moderate (48.1%) compared to the placebo group (38.5%), but there was a higher

frequency of subjects in the placebo group reporting a maximum AE of severe grade (30.8%) compared to the vaccine group (14.8%).

- The most common injection site AE was pain, tenderness, soreness.
- The most common systemic AE headache and pharyngitis.
- One pregnancy occurred in the vaccine group, it led to spontaneous miscarriage [22].

2.4.5 Conclusion

The 80 mcg dose of the HPV 18 L1 VLP vaccine was noted to be immunogenic at 4 weeks postdose 3. The GMTs of anti-HPV antibodies were highest at 1 month after the third dose of vaccine. There was no need for concern regarding the safety evaluation.

2.5 CONCLUSION

These initial studies evaluated the kinetics of vaccine induced anti-HPV responses, demonstrating a priming effect of 2 doses with peak titers achieved at month 7, after which titers declined rapidly to reach a plateau at month 24. They remained stable until month 36. Based on dose-ranging data from protocol 002 and protocol 004, the 40mcg-dose for the HPV 16 vaccine was selected for the first efficacy trial in protocol 005 [19, 20, 21].

A sub study in these early monovalent HPV clinical trials aimed to measure HPV 11 L1-VLP vaccine priming of humoral and cellular immune responses in seronegative, HPV DNA-negative, college-age women. The results of this study showed that Th1 or Th2 cytokines (IFN-γ or IL-5) were detected in response to HPV 11 L1 VLP for all vaccine recipients and none of the placebo recipients tested. The predominant T-cell population with detectable IFN-γ and IL-5 production was the T-cell subpopulation depleted of $CD8^+$ T-cells [19]. The overall HPV-specific T-cell activity was observed as a discrete proliferative response consistent with homeostasis in memory T-cell responses. In addition the immunoglobulin isotype and subclass profiles elicited by vaccination demonstrated the generation of both Th1 and Th2 responses (IgG1 and IgG2).
In a separate sub study the results demonstrated no response prior to vaccination, however post-vaccination strong HPV 16 L1 peptide-specific T-cell responses were observed in all subjects. Vaccination of young females with the quadrivalent HPV L1 VLP vaccine resulted in induction of a strong L1 peptide-specific IFNγ-associated T-cell response and a concomitant B-cell response producing L1 VLP-specific antibodies [19].

Thus it can be concluded that these early monovalent vaccine clinical trials were precursors for development and assessment of safety and effectiveness of quadrivalent HPV vaccine [17,18].

3. QUADRIVALENT HPV VACCINE (GARDASIL/SILGARD) CLINICAL EFFICACY STUDIES

3.1 Introduction

Clinical efficacy was assessed in 4 randomized double-blind placebo-controlled phase II and phase III clinical trials. It included protocols 005, 007, 013 and 015 with a total of 20,877 participants. This included 304 subjects who received monovalent HPV 16 L1 VLP vaccine in study 012, a sub-study of study 013.

Protocol 005 was the proof-of-concept study, evaluating efficacy of a monovalent HPV 16 L1 VLP 40 mcg vaccine. Its primary endpoint was safety and tolerability of the vaccine in 3 doses and efficacy in prevention of persistent HPV 16 infection verses placebo [20,21]. This study was described in detailed in the previous section.

Protocol 007 was the dose-ranging study of the quadrivalent HPV L1 VLP vaccine. It evaluated efficacy of the phase III formulation (20/40/40/20 mcg) in preventing persistent HPV 6/11/16/18-related infection or disease. It also included identification of formulations with specific anti-HPV responses and general tolerability [23].

Protocols 013 and 015 are the essential studies of the efficacy of the quadrivalent vaccine against vaccine HPV-related EGL and CIN.

Protocol 013, also known as **FUTURE I** study, aimed to evaluated efficacy of the vaccine in reducing HPV 6,11,16,18- related genital warts, VIN, VaIN, vulvar or vaginal cancer, CIN, AIS or cervical cancer versus in placebo, as well as safety and tolerability [24].

Protocol 015, also known as **FUTURE II** study, was focused on evaluating efficacy in reducing the incidence of HPV 6,11,16,18-related CIN 2/3, AIS or invasive cervical cancer in HPV naïve subjects, as well as general safety and tolerability [25].

3.2 Objective

Objective of the studies was that administration of the HPV vaccine will reduce the overall incidence of HPV-related cervical and genital disease.

Two types of endpoints were defined:

Persistent HPV infection: used in studies 005 and 007, defined as persistent vaccine-type HPV infections without confirmed CIN infection, with confirmed CIN, histologically confirmed CIN 1, 2, 3, AIS, or cervical carcinoma due to vaccine-type HPV [20, 21, 23].

Disease endpoints were included in all of the studies and defined as the incidence of HPV related CIN 1, CIN 2, CIN 3 or worse, combined incidence of external genital lesions related to vaccine HPV type, combined incidence of condyloma acuminata VIN 1, VIN 2/3, VaIN 1, VaIN 2/3 or worse related to HPV vaccine type and the incidence of AIS, CIN 2/3 or worse related to HPV 16 or HPV 18 [20, 21, 23, 24, 25]

3.3 Method Design

All studies were double-blind, randomised and placebo-controlled trials. All participants received either quadrivalent HPV VLP vaccine or placebo at day 0,month 2 and month 6. Pap tests and cervicovaginal sampling for HPV testing were done every 6 months or every 12 months in study 015 [25].

3.4 Participants

Participants were 16 to 23 year-old females. The studies did not include a screening phase and it included both naïve individuals and individuals who had been exposed to HPV prior to enrolment. At the start of the study all participants were subjected to serum anti-HPV testing, Pap test, cervicovaginal sampling for HPV typing and coloscopy in case of Pap test abnormalities. Regardless of the examination results, participants were randomly placed to either HPV vaccine or placebo group.

Five different populations were defined for HPV-specific efficacy analysis [17, 18]. They are as follows;

Per-protocol efficacy (PPE) population

This population received all 3 doses of the vaccine; at day 1 individuals were seronegative to relevant HPV type(s); during the period from day 1 to month 7 subjects were PCR negative to relevant HPV type(s) and did not have protocol violations.
This population included 64-84% (based on HPV type) of all participants, and it was used as the primary efficacy population.

MITT-populations (modified Intend to Treat Populations)

These populations included the following classified groups and were HPV vaccine type specific.

MITT-1 population which was similar to PPE but it included some violators.
MITT-2 population included HPV vaccine naïve subjects who received at least one dose.
MITT-3 population received at least one injection, Pap test was either normal or abnormal on day 1, and for HPV serology/PCR status was not considered at day 1. This group represents the general female population in this age group.
MITT-4 population included HPV vaccine naïve subjects who received at least 2 doses
RMITT-2 population of HPV naïve and negative Pap test at Day 1 that received at least 1 vaccine dose
RMITT-3 all subjects regardless of baseline HPV status with negative Pap test at Day 1 that received at least 1 vaccine dose

3.5 Results

Overall 19,321 subjects completed the study, accounting for 93% of all subjects who received at least one vaccine dose. In study 005, 84% of patients received 3 injections, while in the other three efficacy studies this percentage ranged from 93% to 98%.

Demographic characteristics such as age, race, geographic region, smoking status, alcohol consumption and history of sexually transmitted diseases were comparable between vaccine and placebo group. Sexual debut occurred at a mean age of 16.7 years, where hormonal contraception was the most common form of contraception [20, 21, 23, 24, 25].

3.5.1 Protocol 005 -Study of Pilot Manufacturing Lot of HPV 16 Virus Like Particle (VLP) Vaccine in the Prevention of HPV 16 Infection

Considering demographic characteristics mean age of participants was 20.1 years. Ethnic distribution was 75% Caucasian, 8.6% blacks, 7.6% Hispanic, 5.9% Asian, 2.0% other, and 1% Native American. Smokers accounted for 25.4% of all participants. The median age of sexual debut of subjects was 17 years.

The primary efficacy endpoint of this study was the incidence of new persistent HPV 16 infection. There were two efficacy analyses. Fixed-case point analysis occurred at a specific pre-determined time point, while final analysis at the end of the 4-year study follow-up [20, 21].

Table 11- *Primary efficacy endpoint- persistent HPV 16 infection.*

Population	HPV 16 vaccine (n= 1193)	Placebo (n= 1198)	Observed Efficacy % (95% CI)
	Number of cases	**Number of cases**	
Fixed Case Analysis			
PPE	0 / 753	41 / 750	100 (90.0,100)
MITT-2	7 / 824	76 / 839	91.0 (80.7, 96.5)
MITT-3	54 / 1004	131 / 1044	59.0 (43.3, 70.7)
End of study Analysis			
PPE	7 / 755	111 / 750	94.3 (87.8, 100)
MITT-2	16 / 824	150 / 839	90.2 (83.5, 94.5)
MITT-3	67 / 1004	217 /1044	70.6 (61.2,78.0)

Source: *L. Koutsky, K. Ault, C. Wheeler et al., A controlled trial of a human papillomavirus type 16 vaccine. New England Journal of Medicine 347 (2002), 1645–1651.*

From the results table shown above, we can see that in the fixed case analysis in the PPE population, all 41 cases of persistent HPV 16 infection were in the placebo group.
At end-of-study, 7 cases in the vaccine group had HPV 16 detected. There were no cases of HPV-related CIN in the vaccine group in the fixed-case or end-of-study analyses. However in the placebo group there were 9 at fixed case analysis and 24 at the end of th study. The MITT-2 results supported those of the PPE analyses [20].

At the end of study in the MITT-3 population, there was a great reduction of HPV 16-related persistent infection and CIN in the vaccine group as compared to placebo. In the vaccine group, 67 subjects were presented with persistent HPV infection, of those 9 patients had HPV 16-related CIN. Meanwhile in the placebo group, 217 participants had persistent HPV infection, out of which 44 patients had HPV 16-related CIN.

This study also showed a significant reduction of HPV 16-related CIN 2/3 or worse in the vaccine group as compared to placebo with vaccine efficacy 77.9% (95% CI: 40.6; 93.4). One-third to one-fourth of the observed HPV infections were of shorter duration than 6

months. Looking at cases longer than 6 months in the MITT-2 analysis reduced the estimates of efficacy, but vaccine efficacy still remained high, with 5 cases in vaccine group versus 88 in placebo group. When assessing infections longer than 12 month in duration, there were 3 such cases in vaccine group versus 43 in placebo group. This demonstrated vaccine efficacy to be estimated at 93.3% (95%CI: 79.1, 100).

Adverse Events

The proportions of subjects with clinical adverse events (AEs), those who discontinued due to AEs or those subjects with systemic AEs were all similar for the vaccine and placebo groups. However, there were slightly more injection site adverse events in the vaccine group as compared to the placebo group. The following table summarizes these results.

In the 15 days after vaccination, the majority of adverse events were rated as mild to moderate in both vaccine and placebo groups. The overall incidences of clinical adverse events were comparable among both groups after dose 1, 2, and 3. There was a slightly higher percentage of subjects reporting an adverse event in both groups after dose 1 (83.3% vaccine, 82.8% placebo) as compared to dose 2 (73.8% vaccine, 69.7% placebo) and dose 3 (74.9% vaccine, 68.4% placebo).

When assessing the injection site reactions, there was a higher proportion of subjects in vaccine group with higher incidence of injection site pain, swelling, and erythema compared to placebo recipients. Both groups were comparable with respect to the proportion of subjects who reported any systemic adverse events within 15 days of vaccination, and the risk differences for specific adverse events were small [20,21].

3.5.2 Protocol 007- A Placebo Controlled Dose-Ranging Study of Quadrivalent HPV Virus Like Particle (VLP) Vaccine

This protocol was a dose-ranging study where the 20/40/40/20mcg dose was used for the evaluation of the vaccine efficacy. The primary endpoint was the incidence of new HPV6/11/16/18-related persistent infection, CIN and/or EGL [23]. The following table is the summary of the results of this study.

Table 12- *Efficacy against HPV 6/11/16/18- related persistent infection or disease (protocol 007)*

	Quadrivalent HPV vaccine (20/40/40/20 mcg) (n = 276)	**Placebo (Aluminum adjuvant) (225 and 450 mcg) (n = 275)**	**Observed Efficacy (95 % CI)**
Primary Endpoint	Number of cases	Number of cases	
Per- protocol	4/235	36/233	89.5 (70.7, 97.3)
HPV 6- related endpoints	0/214	13/209	100.0 (68.2, 100)
HPV 11- related endpoints	0/214	3/209	100.0 (<0, 100.0)
HPV 16- related endpoints	3/199	21/198	86.3 (54.0, 97.4)
HPV 18- related endpoints	1/224	9/224	89.0 (20.5, 99.7)
MITT-2	6/266	48/263	88.5 (73.0, 96.0)
MITT-3	23/268	61/269	64.5 (41.7, 79.0)

Source: *L.Villa, Costa R., Petta C. et al, Prophylactic quadrivalent human papillomavirus (types 6,11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncology (2005) 6: 271-278.*

As can be seen from the table above, in the vaccine group there were 4 endpoint cases, of which 3 were infections without confirmed persistence and 1 of persistent HPV 18 infection. There were no cases of CIN or EGL in the vaccine group, while there were 5 cases in the placebo group.

In the MITT-3 population there were 23 patients with persistent infection in the vaccine group, of whom 3 had HPV-related CIN. Of these two were HPV 16-related CIN 3 and one was HPV 18-related CIN 1 [23].

In the placebo group, there were 61 patients with persistent HPV infection. The following table illustrates the breakdown of each type.

Table 13 - *Breakdown of 61 cases of HPV 6/11/16/18 persistent infection or disease in placebo group.*

EGL = 4	3 condyloma	1 HPV 6-related
		1 HPV 6/16-related
		1 HPV 11-related
	1 VIN 2/3	1 HVP 16-related
HPV-related CIN = 12		1 HPV 6-related CIN 3
		1 HPV 18-related CIN 2
		2 HPV 16-related CIN 1
		3 HPV 16-related CIN 2
		3 HPV 16-related CIN 3
		1 HPV 18-related CIN 1
		1 HPV 18-related CIN 2

Source: *L.Villa, Costa R., Petta C. et al, Prophylactic quadrivalent human papillomavirus (types 6,11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncology (2005) 6: 271-278.*

In this study the preliminary efficacy data was extended up to 5 years. After the end of study at month 36, subjects were re-evaluated at Month 54 and 60 [23]. The following table illustrates results at Month 60 and suggest persistence of efficacy.

Table 14- *Analysis of efficacy against HPV 6/11/16/18- related persistent infection or disease from month 7 (PPE) and from 30 days (MITT-2, MITT-3) through month 60.*

HPV 6/11/16/18 related infection or disesase	**Silgard**	**Placebo**	**Observed Efficacy (95 % CI)**
	Number of Cases	Number of cases	
By study population			
PPE	2 /235	46 /233	95.8 (83.8, 99.5)
MITT-2	4 /266	59 /263	93.7 (83.0, 98.3)
MITT-3	21 /268	74 /269	73.2 (56.1,84.3)

Source*: L.Villa, Costa R., Petta C. et al, Prophylactic quadrivalent human papillomavirus (types 6,11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncology (2005) 6: 271-278.*

A re-analyses of persistent infection lasting more than 6 to 12 months and those lasting more than 12 months were assessed. It was demonstrated that one-third to one-fourth of the observed HPV infections were of shorter duration than 6 months. When looking at cases greater than or equal to 6 months in the MITT-2, this reduced the estimates of efficacy. However, vaccine efficacy was still high one in vaccine group versus 23 in placebo. When looking at periods greater or equal to 12 months there were 0 cases in vaccine group versus 11 cases in placebo group. Thus vaccine efficacy was estimated at 100% with 95% CI: 43.3, 100.

Adverse Events

The proportion of subjects with an AE was slightly higher in the vaccine group a compared to the placebo group. The proportion of subjects with systemic AEs was comparable among the groups, with the most commonly reported headache and pyrexia. The proportion of subjects with injection site AEs was somewhat higher in the vaccine group compare with the placebo group. The most common injection site adverse events were pain, erythema, and swelling. The majority of these events were mild to moderate in severity. There were 7 serious AEs, one of which was fatal, but none were judged to be vaccine related.

3.5.3 Protocol 013- FUTURE I- Evaluation of the Efficacy of Quadrivalent HPV L1 Virus-Like Particles in Reducing the Incidence of HPV 6, 11, 16, and 18 Related External Genital Warts, VIN, VaIN, Vulvar Cancer, and Vaginal Cancer

This study focused on clinical genital disease and had two co-primary efficacy endpoints. The first one was cervical endpoint, showing incidence of HPV 6/11/16/18-related CIN (1,2,3), AIS or cervical cancer. The second endpoint was external genital lesions (EGL) endpoint, that is incidence of HPV 6/11/16/18-related genital warts, VIN, VaIN, vulvar or vaginal cancer [24]. The following results are of the fixed case analysis that occurred 2 years of follow up.

First efficacy endpoint- efficacy against CIN lesions

Analyzing efficacy by HPV type and CIN lesion in the PPE population, it can be seen that most endpoint cases were HPV 16 related (~59%). Approximately half of subjects with a CIN lesion had a pathological diagnosis of CIN 2 or worse. Vaccine efficacy (VE) against CIN 3/AIS was 100% (95% CI (55,100)). No cases of invasive cervical cancer were detected among subjects in any population. In the MITT-2 population, VE was 96.5% with two cases of CIN detected in the vaccine group versus 57 in the placebo group [24]. The following table shows details of these results.

Table 15- *Efficacy by HPV type and by CIN lesion (PPE population) protocol 013.*

Endpoint	**Quadrivalent HPV vaccine (n = 2717)**	**Placebo (n = 2725)**	**Observed Efficacy (95 % CI)**
	Number of cases	Number of cases	
HPV 6/11/16/18-related CIN			
PPE	0/2240	37/2258	100.0 (87.4, 100.0)
MITT-2	2/2557	57/2573	96.5 (86.7, 100.0)
By HPV type			
HPV 6- related CIN	0/1960	7/1975	100.0 (30.3, 100.0)
HPV 11- related CIN	0/1960	3/1975	100.0 (<0, 100.0)
HPV 16- related CIN	0/1887	22/1847	100.0 (82.1, 100.0)
HPV 18- related CIN	0/2101	8/2120	100.0 (41.2, 100.0)
By lesion type			
CIN 1	0/2240	25/2258	100.0 (84.1, 100.0)
CIN 2 or worse	0/2240	20/2258	100.0 (79.7, 100.0)
CIN 2	0/2240	14/2258	100.0 (69.7, 100.0)
CIN 3	0/2240	10/2258	100.0 (55.2, 100.0)

Source: *The FUTURE I Investigators, Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. The New England Journal of Medicine (2007) 356 (19)1928-1943.*

In the MITT-3 population vaccine efficacy of 43% was much lower against the combined endpoint. It was non-significant against CIN 2 or worse as VE 23% and in CIN 3/AIS VE was only 0.2%. The following table summarizes all the results from MITT-3 populations.

Table 16- *Analysis of efficacy against HPV 6/11/16/18- related CIN in MITT-3 population (protocol 013).*

	Quadrivalent HPV vaccine (n = 2717)	**Placebo (n = 2725)**	**Observed Efficacy (95 % CI)**
Endpoint	Number of cases	Number of cases	
HPV 6/11/16/18-related CIN	65/2607	113/2611	42.9 (21.9, 58.6)
By HPV type			
HPV 6- related CIN	4/2607	18/2611	77.9 (32.8, 94.6)
HPV 11- related CIN	0/2607	9/2611	100.0 (49.5, 100)
HPV 16- related CIN	54/2607	79/2611	32.0 (2.6, 52.8)
HPV 18- related CIN	8/2607	22/2611	63.8 (15.5, 86.1)
By lesion type			
CIN 1	41/2607	83/2611	51.0 (27.9, 67.1)
CIN 2 or worse	48/2607	62/2611	22.8 (<0, 48.2)
CIN 2	35/2607	40/2611	12.8 (<0, 46.2)
CIN 3	35/2607	35/2611	0.2 (<0, 39.3)

Source: *The FUTURE I Investigators, Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. The New England Journal of Medicine (2007) 356 (19)1928-1943.*

When considering the HPV vaccine type-related CIN, the cumulative incidence was 4.3% in the placebo and 2.5% in the vaccine group. It can be seen that the vaccine reduced the risk of diagnosis with HPV 6/11/16/18-related CIN from 1/23 to 1/40 over the 2 years of follow-up.

Second Efficacy Endpoint- efficacy against external genital lesions

When observing PPE population, all cases of EGL and of VIN/VaIN 2/3 occurred in the placebo group. In the MITT-2 population VE against HPV6/11/16/18-related EGL was 94.9% (95% CI (84.4, 99.0)).

Table 17- *Efficacy by HPV type and by EGL lesion in PPE population (protocol 013).*

	Quadrivalent HPV vaccine (n = 2717)	**Placebo (n = 2725)**	**Observed Efficacy (95 % CI)**
Enpdoint	Number of cases	Number of cases	
HPV 6/11/16/18-related EGL	0/2261	40/2279	100 (88.4,100.0)
By HPV type			
HPV 6- related EGL	0/1978	23/1991	100 (82.5,100)
HPV 11- related EGL	0/1978	10/1991	100 (55.1,100)
HPV 16- related EGL	0/1890	10/1855	100 (56.3,100)
100HPV 18- related EGL	0/2120	3/2136	100 (<0,100)
By lesion type			
Condyloma, VIN1 or VaIN 1	0/2261	34/2279	100 (88.5,100)
VIN 2/3 or VaIN 2/3	0/2261	7/2279	100 (30.2,100)

***Source**: The FUTURE I Investigators, Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. The New England Journal of Medicine (2007) 356 (19)1928-1943.*

In the MITT-3 population VE of 68% against combined incidence was significant, despite EGL cases that were observed. However, VE was non-significant against VIN/VaIN 2/3. Cumulative incidence of HPV 6/11/16/18-related EGL was 3% in the placebo group and 1% in the vaccine group. Vaccination reduced the risk of EGL diagnosis from 1/33 to 1/103 over the 2 years of follow-up [24].

Table 18-*Efficacy by HPV type and by EGL lesion in MITT-3 population (protocol 013)*

	Quadrivalent HPV vaccine (n = 2717)	**Placebo (n = 2725)**	**Observed Efficacy (95 % CI)**
Enpdoint	Number of cases	Number of cases	
HPV 6/11/16/18-related EGL	26/2671	80/2668	67.8 (49.3,80.1)
By HPV type			
HPV 6- related EGL	19/2671	51/2668	63.0 (36.2, 79.4)
HPV 11- related EGL	2/2671	16/2668	87.5 (47.9,98.6)
HPV 16- related EGL	5/2671	19/2668	73.8 (27.3, 92.3)
HPV 18- related EGL	1/2671	8/2668	87.5 (7.0, 99.7))
By lesion type			
Condyloma, VIN1 or VaIN 1	22/2671	72/2668	69.7 (50.6, 82.1)
VIN 2/3 or VaIN 2/3	4/2671	11/2668	63.7 (<0,91.6)

Source: *The FUTURE I Investigators, Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. The New England Journal of Medicine (2007) 356 (19)1928-1943.*

Adverse Events

The overall proportion of subjects who experienced at least one AE was slightly higher in the vaccine group, as well as those reporting a local AE compared to placebo recipients. The proportion of subjects with a systemic AE and the proportions of subjects with serious AEs were comparable between the vaccine and placebo groups. Few subjects discontinued due to an AE. One vaccine recipient and two placebo recipients died during the study, none of the deaths were vaccine related. Most subjects reported adverse experiences with the maximum intensity of mild or moderate.

3.5.4 Protocol 015- FUTURE II- Study to Investigate the Safety, Immunogenicity, and Efficacy on the Incidence of HPV 16/18 Related CIN 2/3 or Worse of the Quadrivalent HPV L1 Virus Like Particle (VLP) Vaccine

This study's was focused on vaccine efficacy against HPV 16/18-related high-grade cervical lesions. Its primary endpoint was the combined incidence of HPV 16- or 18-related CIN 2, CIN 3, AIS or cervical cancer. This analysis of vaccine efficacy showed 100% efficacy in the PPE population [25].

Table 19- *Interim analysis of efficacy against HPV 16/18 related CIN 2/3 in PPE population (protocol 015)*

	Quadrivalent HPV vaccine (n = 6082)	**Placebo (n = 6075)**	**Observed Efficacy (95 % CI)**
Primary Endpoint	Number of cases	Number of cases	
HPV 16/18- related CIN 2/3 or worse	0/5301	21/5258	100 (75.8,100.0)
By HPV type			
HPV 16- related CIN ≥ 2/3	0/4552	16/4405	100 (74.8,100)
100HPV 18- related CIN ≥ 2/3	0/5051	8/4968	100 (42.3,100)
By lesion type			
CIN 2	0/5301	15/5258	100 (72.3,100)
CIN 3/AIS	0/5301	16/5258	100 (74.2,100)
Cervical cancer	0/5301	0/5258	Not available

Source: *The FUTURE II Study Group, Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions, New England Journal of Medicine 356 (2007), pp. 1915–1927.*

The efficacy in the MITT-2 population was 97% and it was supportive of the PPE results. Regarding the cases with CIN in both groups in the MITT-2 population, it must be noted that these subjects became infected with vaccine HPV types during the vaccination period prior to Month 7 [25].

In the MITT-3 population the magnitude of efficacy was substantially lower, but still significant against CIN 2 (VE: 51%) and CIN 3/AIS (VE: 44%). In comparison with MITT-2, there were 141 additional cases, where great majority of them occurred among subjects who were HPV 16 and 18 PCR positive and/or seropositive at baseline.

Over a 2-year follow-up the cumulative incidence of HPV16/18-related CIN 2/3 in the placebo and vaccine group were 1.9% and 1.1%, respectively with a total of 1 in 54 subjects and 1 in 89 subjects, respectively, developing such a lesion.

Table 20- *Summary of primary efficacy analysis in the MITT population (protocol 015)*

	Quadrivalent HPV vaccine (n = 6082)	**Placebo (n = 6075)**	**Observed Efficacy (95 % CI)**
Primary Endpoint	Number of cases	Number of cases	
HPV 16/18- related CIN 2/3 or worse			
PPE	0/5301	21/5258	100 (75.8,100)
MITT-2	1/5736	36/5766	97.2 (83.4,100)
CIN 2	1/5736	28/5766	96.3 (77.4,100)
CIN 3/AIS	0/5736	27/5766	100 (85.2,100)
MITT-3	67/5947	111/5973	39.2 (16.9,55.8)
By HPV type			
HPV 16-related CIN	62/5947	99/5973	36.9 (12.4,54.8)
HPV 18-related CIN	5/5947	22/5973	77.1 (38.0,93.2)
By lesion type			
CIN 2	36/5947	74/5973	51.0 (26.0,68.0)
CIN 3/AIS	47/5947	85/5973	44.3 (19.5,61.8)
Cervical cancer	0/5947	0/5973	Not available

Source: *The FUTURE II Study Group, Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions, New England Journal of Medicine 356 (2007), pp. 1915–1927.*

Adverse Events

Slightly more subjects in the vaccine group experienced one or more AEs compared to the placebo group. There were somewhat more injection site AEs in the vaccine group compared to the placebo group, although the rates of systemic AEs were similar in both groups [25].

3.6 . Discussion

3.6.1 Supplementary Analyses- Pooled Data and Meta-Analyses

These meta analyses pooled data from all four quadrivalent vaccine trials (005,007,013,015) in order to asses cumulative vaccine efficacy against both CIN and EGL diseases [17,18].

The first assessment was combined analyses in PPE that showed statistically significant vaccine efficacy against both vulvar and vaginal condyloma acuminata, VIN 1, VIN 2/3 and VaIN 1. The majority of condyloma was HPV 6 and 11-related vulvar condyloma. The summarized results are shown in the table below.

Table 21- *Analysis of efficacy against HPV 6/11/16/18-related EGL by disease severity, PPE population (Protocols 007, 013, 015)*

	Quadrivalent HPV vaccine (n = 6082)	**Placebo (n = 6075)**	**Observed Efficacy (95 % CI)**
	Number of cases	Number of cases	
HPV 6/11/16/18-related condyloma	1/7897	91/7899	98.9 (93.7,100)
Vulvar condyloma	1/7897	88/7899	98.9 (93.5,100)
Vaginal condyloma	0/7897	8/7899	100 (41.4, 100)
HPV 6/11/16/18-related VIN 1	0/7897	10/7899	100 (55.4, 100)
HPV 6/11/16/18-related VIN 2/3	0/7897	8/7899	100 (41.4, 100)
HPV 6/11/16/18-related VaIN 1	0/7897	7/7899	100 (30.6, 100)
HPV 6/11/16/18-related VaIN 2/3	0/7897	5/7899	100 (<0, 100)

Source*: Silgard, Scientific Discussion, European Medicines Agency. September, 2007. http://www.emea.europa.eu/humandocs/Humans/EPAR/silgard/silgard.htm*

In the combined analysis when assessing vaccine efficacy against HPV 16/18-related VIN 2/3 and VaIN 2/3, it was statistically important only in the MITT-2 population. In this population VE was 100%, and it was lower in the MITT-3 population. This can be seen in the results of the table below.

Table 22- *Analysis of efficacy against HPV 16/18 related VIN 2/3 and VaIN 2/3 (protocols 007,013,015)*

	Quadrivalent HPV vaccine (n = 9075)	**Placebo (n = 9075)**	**Observed Efficacy (95 % CI)**
	Number of cases	Number of cases	
Per-Protocol population			
HPV 16/18- related VIN 2/3	0/7769	5/7741	100 (<0,100)
HPV 16/18- related VaIN 2/3	0/7769	5/7741	100 (<0,100)
MITT-2			
HPV 16/18- related VIN 2/3	0/8641	17/8667	100 (75.6, 100)
HPV 16/18- related VaIN 2/3	0/8641	7/8667	100 (30.3, 100)
MITT-3			
HPV 16/18- related VIN 2/3	7/8954	18/8962	61.0 (2.1,86.2)
HPV 16/18- related VaIN 2/3	2/8954	9/8962	77.7 (<0,97.7)

Source: *Silgard, Scientific Discussion, European Medicines Agency. September, 2007. http://www.emea.europa.eu/humandocs/Humans/EPAR/silgard/silgard.htm*

Integrated summary of efficacy –HPV 6/11/16/18-related CIN and EGL of all grades

An integrated summary of vaccine efficacy with respect to CIN and EGL was based on outcomes in studies 007, 013 and study 015, and it used data from study 005 only for HPV 16-related CIN. A total of 20,887 women were included in this summary report with focus on the incidence of HPV 6/11/16/18-related CIN and EGL of all grades. When assessing CIN endpoints, the integrated data showed that the vaccine in the PPE population reduced the incidence of HPV 6/11/16/18-related CIN/AIS, with VE 95.2% Specifically, regarding the CIN 1 incidence caused by vaccine HPV types VE was demonstrated at 93.1 % while for CIN 3/AIS caused by vaccine HPV types it was optimal at 100%. This percentage of VE was much lower in MITT-3 population, and the results are summarized in the table below [17,18,27].

Table 23- *Comparison of VE against CIN diseases among PE and MITT-3 populations.*

	PPE			**MITT-3**		
	Vaccine	**Placebo**	**VE (95% CI)**	**Vaccine**	**Placebo**	**VE (95% CI)**
HPV 6/11/16/18-related CIN/AIS	4	83	95.2% (87.2, 98.7)	170	317	46.4% (35.2, 55.7)
CIN 1 caused by vaccine HPV types	4	58	93.1% (81.4, 98.2)	97	213	54.4% (41.8, 64.5)
CIN 3/AIS	0	26	100% (84.8, 100)	84	126	33.1% (11.1, 49.8)

***Source**: Silgard, Scientific Discussion, European Medicines Agency. September, 2007. http://www.emea.europa.eu/humandocs/Humans/EPAR/silgard/silgard.htm*

The vaccine efficacy appeared comparable with respect to each HPV type included in the vaccine.

When assessing EGL endpoints, the integrated data from all efficacy studies showed that the HPV vaccine in the PPE population reduced the incidence of HPV 6/11/16/18-related EGLs with VE of 99.1% . Most importantly it prevented the development of VIN 2/3 or VaIN 2/3 caused by vaccine HPV types at 100% VE. The vaccine efficacy against EGL endpoints in the MITT-3 population was considerably lower and can be seen in the table below.

Table 24- *Comparison of VE against EGL among PE and MITT-3 populations*

	PPE			**MITT-3**		
	Vaccine	**Placebo**	**VE (95% CI)**	**Vaccine**	**Placebo**	**VE (95% CI)**
HPV 6/11/16/18-related EGLs	1	113	99.1% (95.0,100.0)	68	229	70.4% (61.0,77.7)
HPV 6/11/16/18-related VIN 2/3 or VaIN 2/3	0	13	100% (67.2, 100)	8	30	73.3% (40.3, 89.4)

Source: *Silgard, Scientific Discussion, European Medicines Agency. September, 2007. http://www.emea.europa.eu/humandocs/Humans/EPAR/silgard/silgard.htm*

The majority of the VIN/VaIN 2/3 were caused by HPV 16/18 types. It is seen in the PPE in 10 out of 13 cases, while in the MITT-3 all 8 vaccine and 26 out of 30 placebo cases were HPV 16/18 type related.

Genital warts predominated among EGLs. The vaccine efficacy against HPV 6/11/16/18-related genital warts (+ VIN/VaIN 1) was demonstrated as 99% (95% CI: 94.4, 100). While VE against genital warts caused by HPV 16/18 is 100% (95% CI: 83.4, 100) in PPE population. VE in the MITT- 3 population was 70.1% and 69.1%, respectively.

Combined interim efficacy analysis - HPV 16/18-related CIN 2/3

In this combined analysis from all 4 trials, the efficacy of the quadrivalent vaccine in preventing cervical cancer was evaluated with HPV 16/18-related CIN 2/3 and AIS as the composite endpoint. This study involved analysis of 20,541 subjects.

Fifty three cases of CIN 2/3 or worse were observed, and all occurred in the placebo group, with the vaccine efficacy accounting for 100% in the PPE group. As seen in other analyses, VE in the MITT-3 population was lower accounting for 39%. The table below shows further details of this meta analysis.

Table 25- *Efficacy against HPV 16/18- related CIN 2/3 or worse in PPE population (Protocols 007,005,013,015)*

Study population	**Quadrivalent HPV vaccine (n = 10268)**	**Placebo (10273)**	**Observed Efficacy (95% CI)**
	Number of cases	Number of cases	
Per-Protocol			
Combined protocols	**0/8487**	**53/8460**	**100 (92.9, 100.0)**
Protocol 005	0/755	12/750	100 (65.1, 100.0)
Protocol 007	0/231	1/230	100 (<0.0, 100.0)
Protocol 013	0/2200	19/2222	100 (78.5, 100.0)
Protocol 015	0/5301	21/5258	100 (80.9, 100.0)
By HPV type			
HPV 16	0/7393	44/7200	100 (91.5, 100.0)
HPV 18	0/7376	14/7312	100 (70.1, 100.0)
By lesion type			
CIN 2	0/8487	36/8460	100 (89.3, 100.0)
CIN 3/ AIS	0/8487	32/8460	100 (87.9, 100.0)
MITT-3			
Combined protocols	**122/9831**	**201/9896**	**39.0 (23.3,51.7)**
By lesion type			
CIN	76/9831	131/9896	41.8 (22.1,56.7)
CIN 3/ AIS	85/9831	134/9896	36.3 (15.7, 52.0)

Source: *Silgard, Scientific Discussion, European Medicines Agency. September, 2007. http://www.emea.europa.eu/humandocs/Humans/EPAR/silgard/silgard.htm*

It must be noted that most of the CIN 2/3 cases were caused by HPV 16, but comparable vaccine efficacy could be demonstrated for HPV 18. The results in relevant MITT-1 and MITT-2 populations were supportive of the primary PPE conclusion [17,18,27].

Population benefit integrated summary of efficacy

The population benefit of the HPV vaccine was measured in terms of the vaccine's impact on the overall rates of CIN and EGL disease due to any HPV type, incidence of Pap test abnormalities, and cervical procedures.

In the RMITT-2 population there was a significant reduction in the risk of CIN 2 or worse by 37.9%, while that for CIN 3 or worse was 45.5% and for EGL it was 66%. Vaccinated individuals in this study population showed a reduction in number of coloscopies, cervical biopsies, and cervical definitive therapies, compared to individuals from the placebo group. Results observed in the MITT-3 population were consistent, but the impact of the vaccine was lower. In the RMITT-3 and MITT-3 populations there was no established vaccine efficacy against CIN 2 or worse [27].

4. DISCUSSION

4.1 Clinical Efficacy Discussion

Clinical data obtained from the previously mentioned clinical trials clearly show the prophylactic efficacy of quadrivalent HPV vaccine in 16- to 23-year old females in preventing the incidence of HPV16/18-related CIN 2/3 or AIS and HPV 6/11/16/18-related external genital warts.

The efficacy results were consistent among studies and showed that the vaccine was highly efficacious against HPV 6/11/16/18-related CIN and EGLs in the PPE population. In the two important trials, FUTURE I and II, the quadrivalent vaccine was shown to prevent 100% of high-grade cervical pre-cancers (CIN 2/3) and non-invasive cervical cancers (CIN 3/adenocarcinoma in situ (AIS)). As well it proved efficacious against low-grade cervical lesions (CIN 1) in the PPE. With regard to HPV 16/18-related VIN 2/3and VaIN 2/3, there were not enough cases in the PPE population to establish protective efficacy, however all cases occurred in the placebo group [24, 25]. .

Consistent results were obtained in three MITT populations, but the vaccine efficacy was much lower in the MITT-3 population than that of others. MITT-3 represented the general female population with or without HPV disease at start, where vaccine efficacy was 51% against CIN 2 and 44% against CIN 3/AIS. In this population vaccine efficacy against vulvar and vaginal dysplastic lesions was substantially lower. The MITT-2 population represented the primary target population. Consistent and statistically significant results showed VE of 100% against VIN 2/3 and VaIN 2/3 in this population. It must also be noted that the vaccine has not shown any therapeutic efficacy in seronegative/PCR positive subjects [17,18,25,27].

Regarding the immunogenicity, we can see that the anti-HPV responses were higher in younger individuals. Thus immunogenicity was related to age and showed a linear correlation. This was observed in 4 weeks post-dose 2 and 3 periods, where higher GMTs

were in younger 9-15 year old group compared to older 16-26 year old group. At Month 18 GMTs remained 2- to 2.5-fold higher in adolescents compared with GMTs in adult women. The kinetics of immune responses up to Month 18 were similar in both groups. As well, month 7 anti-HPV levels were significantly higher in younger individuals below 12 years of age than in those above that age. Considering GMT and seroconversion rates, it must be noted that the results of the statistical analyses showed that vaccine induced non-inferior immune responses in the adolescent cohort compared with young adult women. These modeling studies also showed that anti-HPV levels in adolescents will remain higher than those associated with protective efficacy in adults over the long-term [19, 22].

Currently, the efficacy of the HPV vaccine in virginal subjects can not be evaluated and we must rely on bridging of data from young adult women to the pre-adolescent girls. It will take a decade or two in order to assess durability of response and long term persistence of efficacy and immune response. Further studies will need to be done in order to asses whether or not a booster dose is required in order to maintain effective immunogenicity, as well whether immunization of the males will be needed to stop the HPV infection cycle.

Currently there are no data on the possible correlation between immunogenicity and efficacy of the quadrivalent vaccine in males. HPV-related infection and disease in men and women share many similarities, but there are some differences such as lower prevalence of specific HPV types and lower antibody response to natural HPV infection in men. Data from Gardasil clinical trials were able to only demonstrate that HPV vaccine induces an immune response in males and is well tolerated [27].

4.2 Discussion of safety of the vaccine

Data compiled from the quadrivalent vaccine clinical trials has shown that overall more subjects which received the vaccine reported an adverse event. This was primarily due to a higher incidence of injection site reactions. There was also more reported systemic adverse events among those who received Silgard as compared with placebo.

Looking at the incidence and types of systemic adverse events (AEs) reported, they were generally similar between the 2 vaccination groups. Pyrexia, respiratory disorders, infections and nervous system disorders were most common, and most of these AEs were moderate in severity. The following table gives an overview of reported systemic AE reactions by organ class in protocols 007, 011, 012, 013 and 015.

Table 26- *Percentage of subjects with systemic clinical AE by system organ class (days 1 to 15 following any vaccination visit).*

	Silgard				Placebo n= 4064			
	All AEs		VR		All AEs		VR	
	N	%	N	%	N	%	N	%
Subjects in analysis population	6160				4064			
Subjects without follow up	91				70			
Subjects with follow up	6069				3994			
Number (%) of subjects with one or more systemic AEs	3591				2414	60.4		
Number (%) of subjects with no systemic AEs	2478				1580	39.6		
Ear &Labyrinth Disorders	70	1.2	24	0.4	38	1.0	14	0.4
Eye disorders	54	0.9	9	0.1	49	1.2	9	0.2
GIT disorders	1051	17.3	418	6.9	730	18.3	313	7.8
General disorders and Site Injection conditions	1116	18.4	817	13.5	726	18.2	515	12.9
Infections & infestations	1046	17.2	184	3.0	735	18.4	143	3.6
Injury, Poisoning & Procedural complications	143	2.4	6	0.1	85	2.1		
Musculoskeletal and Connective Tissue Disorders	499	8.2	191	3.1	352	8.8	137	3.4
CNS disorders	1782	29.4	1257	20.7	1231	30.8	877	22.0
Psychiatric Disorders	106	1.7	31	0.5	77	1.9	23	0.6
Reproductive System Disorders	352	5.8	41	0.7	266	6.7	44	1.1
Respiratory Thoracic and Mediastinal Disorders	490	8.1	96	1.6	321	8.0	77	1.9
Skin and Subcutaneous Tissue Disorders	210	3.5	76	1.3	143	3.6	53	1.3

Note = % are calculated based on the number of subjects with follow-up

VR= vaccine related

Source: *Miller B.N, Food and Drug Administration, Clinical Review of Biologics License Application for Human Papillomavirus 6, 11, 16, 18 L1 Virus Like Particle Vaccine (S. cerevisiae) (STN 125126 GARDASIL), manufactured by Merck, Inc.*

4.2.1. Immunological adverse events

Immunological events such as anaphylactic reaction, bronchospasm or wheezing and urticaria were reported. There was one severe adverse anaphylactic reaction that occurred in the placebo group. Five cases of bronchospasms occurred, one in placebo and four in the vaccine group, of which three were in moderate and one in severe intensity. Urticaria was the most prevalent in placebo group than in vaccine group, 28 vs. 12. Five from the placebo and one from the vaccine group were severe in intensity.

4.2.2. Serious adverse event/deaths/other significant events

Proportions of subjects reporting serious adverse events was small and comparable between vaccination and placebo groups. The most common serious AE in both groups were infections and pregnancy. The following table shows a list of serious vaccine related AEs in safety populations from protocols 007,011, 012,013,015,016 and 018.

Table 27- *Overview of female participants with serious vaccine related adverse events in protocols 007,011,012,013,015,016 and 018.*

Age of 1st vaccination in years	Day from start of trial	Dose number	Day of onset post-dose	AE	Duration of AE	Intensity/ Size	Vaccine relation	Outcome
Silgard								
20	162	3	1	Bronchospasm	2 days	Severe	Possible	Recovery
22	47	2	5	Gastroenteritis	15 days	Severe	Possible	Recovery
22	156	3	1	Headache; hypertension	5 days 1 day	Severe	Definite	Recovery
21	43	2	1	Injection site joint movement impairment; Injection site pain	5 months	Moderate	Probable	Recovery
13	26	1	26	Vaginal hemorrhage	1.7 months	Moderate	Probable	Recovery
13	223	3	42	Vaginal hemorrhage	2.3 months	Moderate	Probable	Recovery
Placebo								
20	58	2	1	Hypersensitivity	3 days	Moderate	Possible	Recovery
21	54	2	1	Chills Headache Pyrexia	1 day	Moderate	Possible	Recovery

***Source**: Miller B.N, Food and Drug Administration, Clinical Review of Biologics License Application for Human Papillomavirus 6, 11, 16, 18 L1 Virus Like Particle Vaccine (S. cerevisiae) (STN 125126 GARDASIL), manufactured by Merck, Inc.*

There were 14 deaths in total during the course of the study, however none were thought to be vaccine related.

4.2.3 Discontinuation

Approximately 0.1% of subjects in each vaccination group withdrew from the study due to an adverse experience [17, 27].

4.2.4 Special Groups

Males

The vaccine was tested on males 9 to 15 years of age at the start of the study. The proportion of subjects reporting any adverse experience and any injection-site adverse event were higher in the vaccine group compared with the non-aluminium-containing placebo group.

Males in the vaccine groups reported injection-site AEs and systemic AEs more than their placebo counterparts. The most common systemic reactions were headache, pyrexia, diarrhea and pharyngo-laryngeal pain [17, 27].

Pregnancy

Currently there are no theoretical concerns regarding teratogenic safety of the Gardasil vaccine or placebo adjuvant, however no clinical studies have been done on pregnant subjects. During the course of immunization with the quadrivalent vaccine, total of 2,266 women (vaccine: 1,115 vs. placebo: 1,151) reported at least one pregnancy. Among these pregnancies outcomes were known for 78.1% of all pregnancies. With few exceptions, the pregnancies with unknown outcomes represented either ongoing pregnancies or subjects that discontinued or were lost to follow-up [17, 27].

Live born infants

The number of live births that were accompanied by other medical conditions was slightly higher in the vaccine group than in the placebo group. The most common medical condition observed during the neonatal period other than congenital anomaly were pre-maturity, neonatal respiratory distress symptom and neonatal jaundice[17, 27].

Congenital anomalies

The number of live births that resulted in congenital anomalies was slightly higher in the vaccine group compared with the placebo group. However, the number of pregnancies that resulted in a congenital anomaly was small and well within the 3-4% incidence reported in studies of pregnancy in large-scale health care systems.

No trend of specific effect on any organ system in relation to the week of gestational development could be observed. It was concluded that the congenital anomaly events were not associated with exposure to the vaccine or to aluminium-placebo adjuvant [17, 27]..

Spontaneous abortion

In the pregnancies that started 30 days within vaccination period, the number that resulted in spontaneous pregnancy loss was lower in subjects who received the vaccine (23.1%) as compared to subjects who received placebo (28.3%). The opposite pattern was seen in pregnancies with start after 30 days from any vaccination (34.2% in vaccine vs 31.9% in placebo group) [17, 27]..

Vaccine administration to lactating women

A total of 995 subjects (500 in vaccine and 495 in placebo group) were breastfeeding during the vaccination period. In the subjects with serious, vaccine related clinical adverse events, 4 subjects, 2 subjects and 1 subject had at least 1 serious adverse experience that was determined to be possibly, probably, or definitely related to the vaccine, respectively. A total of 3.4% of breast feeding infants to mothers in vaccine group and 1.8% infants of mothers in placebo groups experienced a serious adverse event. None of these were judged to be related to the vaccine [17, 27].

4.2.5 Concluding remarks

There were no major vaccine related concerns over safety in either vaccine or placebo group. No anaphylactic shocks or deaths were judged to be related to the administration of the vaccine. Pyrexia, pain, erythema and swelling at the injection site were the most common symptoms observed in both groups. Injection site pain was more common in the vaccine group compared to placebo. It was also determined that vaccine had no impact on the outcome of the pregnancy or fertility, however no studies were done to assess teratogenicity. Vaccination should, therefore, be postponed until after completion of pregnancy. Vaccination should, therefore, be postponed until after completion of pregnancy [17, 27].

III. PHARMACOECONOMICS- RECCOMENDATIONS FOR SUCCESSFUL VACCINATION PROGRAMS

1. INTRODUCTION

Implementation of a national vaccination program requires several steps to be completed in order for it to be successful. First a vaccine must be reviewed by a national control authority for its safety and effectiveness, then it is further reviewed by expert advisory bodies for immunization, and lastly vaccine funding is determined. Other aspects such as vaccine purchase and supply, delivery of vaccination service, coverage and reimbursement, surveillance of the program, immunization financing policies and political will, must be all interlinked together to ensure successful vaccination program at the national level. Target populations and a need for a booster dose in HPV vaccination programs are factors that need to be determined. The efficacy and cost-benefit analysis of newly introduced HPV vaccination programs need to be assessed in the next couple of decades. However, currently we can rely on mathematical models for the possible benefits of the vaccination programs. National HPV vaccination programs are still in early stages and will require further changes to maximize benefits of the program.

2. NATIONAL STRATEGY

Licensing of a vaccine is the first step in implementing a new vaccine into the society. All countries have a national control authority that licenses vaccines. These authorities evaluate the data from clinical trials in order to determine safety and efficacy of vaccines. In Europe vaccines are licensed according to standards of the European Agency for the Evaluation of Medicinal Products (EMEA). Health ministry of each European country further reviews data from EMEA and makes decisions about implementation of the program and allocation of the resources. In Canada, Canadian food inspection agency and the Biologics and Genetic Therapies Directorate of Health Canada are responsible licensing bodies. Meanwhile in United States, Federal Drug Agency (FDA) reviews data from clinical trials and is responsible for licensing. Expert advisory bodies are required in each country to advise national immunization programs regarding which vaccines should be implemented and their vaccination schedules. In most countries this is done by ministry of health, depending whether the immunization program is private or public [31].

Allocations of monetary funds for immunization programs is the most challenging element of implementation of successful national vaccination programs. Vaccination programs are funded by both public and private sectors, varying in amounts in different countries. In many EU countries adult vaccination is available through private sector, where a patient hast to pay full cost, while infant vaccination programs are funded by the government. The same is seen in North America, where Canadian government funds children's vaccination programs, while adults are reimbursed by the health insurance companies.

After these three points are assessed further structural organization is needed to realize the goal of successful vaccination programs. The following interrelated components must be considered, vaccine purchase and supply, service delivery, high reimbursement rates, surveillance of vaccine coverage, effectiveness and safety and political willingness.

Vaccine purchase and supply

Government plays an important role in most of these steps. Besides financing vaccination its role is to arrange contracts with manufacturers for reduced rates for vaccines. The costs of visiting the provider, administrative costs, and adequate supply of vaccines must also be taken into an account. There is also a competition for government's funding approval between HPV vaccine and other vaccines, however vaccination programs are most often cost-effective, at least from a societal perspective [31].
Gardasil is one of the most expensive vaccines, with a non-discounted price for three doses is $360 US. The high cost of the first generation of this quadrivalent HPV vaccine may provide a large barrier to introduction into the world's poorest countries, where it is needed the most [33].

Delivery of vaccination service

It has been shown in the past that the most successful vaccination programs are implemented at the school level, such as HBV vaccination. Canadian government has recently made a decision to fund school based Gardasil vaccination programs. It is a voluntary, free service provided to all grade 8 girls, and this initiative represents government's investment of $117 million over three years [38].

In countries where there is a lack of school vaccination programs, doctors will play a major role in education young adolescents about potential benefits of HPV vaccination. They will also be a primary source for HPV vaccination for sexually active adult women. Therefore, many countries will need to rapidly develop new vaccination strategies to reach the largest amount of women [31].
Administration costs will vary within each country and region. Few countries have universal preadolescents health care programs, therefore the costs of establishing and maintaining a new system for HPV vaccination are likely to be significant. However, if vaccines could be given at an earlier age, together with other vaccines, the costs could be significantly reduced [32].

Education of the general public

While the concerns for safety and efficacy are present, the major parental determining factor is poverty rates. Low educational, socioeconomic status and large family size are critical barriers to vaccination. Government as well as physicians will need to educate and inform parents about recommendations, safety, efficacy, risks and benefits of vaccination programs. Regarding HPV vaccine, this will also include raising awareness in general population about the links of cervical cancer with HPV infection, as well as acceptability in society of vaccinating young girls against a sexually transmitted disease [30].

Continuing education of the gynecologists will also play an important role in relaying the most accurate up to date information to the general public. Attitudes of medical professionals regarding HPV vaccination has shown to vary, and there are still gaps in their knowledge regarding the HPV infection. For example, a recent Canadian survey has shown that a significant proportion of general practitioners and pediatricians wrongly associated anogenital warts induced by HPV6 and HPV11 with cervical cancer precursors. This may result in sending a wrong message to their patients. In addition, more than one third of respondents overestimated the proportion of cervical cancer related to HPV16 and HPV18, which may lead to over estimation of expected vaccine impact [29].

One of the most efficient ways to implement a vaccination program at a national level is to introduce it at the school levels. While vaccinations against viruses such as HBV are obligatory in school settings, HPV remains to be voluntary school program, where parents decide whether their child is vaccinated. This approach has been highly effective in increasing coverage rates and preventing disease [39].

Funding of vaccination programs

Government funding, coverage rates and reimbursement are the major limit to HPV vaccination programs. Since HPV vaccine is targeted at adolescent girls, a parental approval will be a major factor influencing the success of vaccination programs once they are implemented [31].

Support of the policy makers remains to be the most influential factor regarding allocation of public funds for vaccination programs. Some policy makers tend to be skeptical regarding introduction of new vaccination programs due to inadequate data as to whether the burden of a targeted disease is sufficient to approve the introduction of a new vaccine. Even though HPV associated diseases cause a burden on the society, the efficacy of the vaccination programs remains to be seen in the next few decades. This is due to the fact that it will take 20-30 years for vaccinated adolescents to reach the adult ages where incidence of cervical cancer is highest. Demonstration of reduced risk in these populations will be a key factor of influencing policy makers to allocate resources into HPV vaccination programs. The evaluation of different alternatives and costs of cervical screening programs will also be contributing factors [32, 33].

3. IDENTIFICATION OF TARGET POPULATIONS FOR HPV VACCINATION PROGRAMS

Current available scientific data indicates that the target population is young adolescent girls. This data varies in different countries, due to differences of available vaccination, age of sexual debut and epidemiology. However, this data is still inadequate in identifying the optimal target populations for the HPV vaccine. Further clinical studies are needed to assess whether the vaccine is effective in women over the age of 25, sexually active women as well as effectiveness in males [31,32,33].

Since HPV vaccines are prophylactic vaccines, they need to be given to young girls before the onset of sexual activity where there is a decreased risk of acquiring HPV infection. The age of onset of sexual activity varies between countries and between the two sexes as shown in the following table.

Table 28- *Age of onset of sexual activity in females and males in various countries*

Country	Average age 1st sex		Percentage of 18-year-old	
	Females (years)	Males (years)	Females (%)	Males (%)
Czech Republic	15	17	NA[b]	NA[b]
Finland	16	18	68	50
France	18	17	49	66
Germany	17	17	56	57
Iceland	16	16	63	73
Italy	20+	19	NA[b]	NA[b]
Portugal	19	16	25	68
Spain	17	17	NA[b]	NA[b]
United Kingdom	18	18	64	64
United States	16	NA[b]	63	73

NA= data not available

Source: *T. C. Wright, P.V. Dammeb, H. Schmitt, A. Meheusd, Chapter 14: HPV vaccine introduction in industrialized countries, Vaccine 24S3 (2006) S3/122–S3/131.*

Due to these differences, the optimal age for vaccinations will vary within each country. As well, the level of protection of the vaccine at particular age group will depend on percentage of children that have had sex [33].

Data from phase III clinical trials has shown prophylactic value of quadrivalent HPV vaccine in young females 15–25 years of age who are DNA and serologically negative for the specific HPV vaccine types. This data was used to perform immunological bridging studies to demonstrate efficacy of the vaccines in boys and girls between 9 and 14 years of age and in 25–55 year-old females [31].

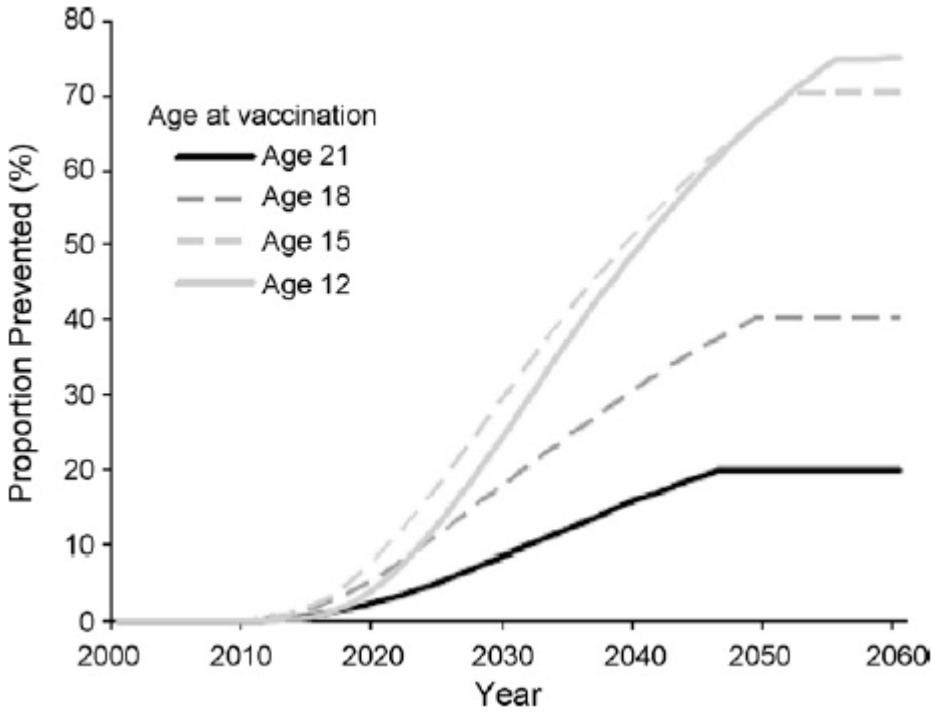
Identification of optimal target population becomes most problematic when it comes to allocating monetary funds. One viewpoint is that the HPV vaccination is likely to be relatively expensive and will be most effective when administered to young girls 9 to 13 years of age, prior to sexual debut. The other view argues that many sexually active adolescents and women will benefit from vaccination. Their argument lies in the results obtained from phase III clinical trials that involved sexually active women (94% of participants). The results showed that 71% of the participants did not have exposure to vaccine HPV types 6, 11 ,16 or 18. This view reasoned that the vast majority of sexually active young women would receive some benefit from "catch-up" immunization. Further clinical trials aimed at evaluating efficacy of the vaccine in this age group as well as sexually active individuals will be needed to accurately identify all target groups [31,33].

4. BOOSTER DOSE

Clinical trials have shown that both bivalent and quadrivalent vaccines produce higher levels of neutralizing antibodies, than those found in natural infections. Follow up after 42 months has been shown consistent levels. During the following years it will need to be assessed whether booster vaccinations will be necessary, and whether or not the current vaccines are able to trigger immune memory [33].

Vaccination programs are aimed currently at young adolescents, so it will take couple of decades before any impact of vaccination no cervical cancer rate is observed. Full effects of vaccination on cancer rates may not be observed for up to another 50 years, as shown in the following figure.

Picture 5- *Projected outlook of proportion of HPV infection prevention by vaccination among various age groups.*



Source: *Harper D., Paavonen J.,Age for HPV vaccination, Vaccine (2008) 26S, A7-A11.*

COST-BENEFIT ANALYSES

Currently, there are very few cost-benefit and cost-effectiveness analyses done. The statistical modeling techniques such as Markov, will play a crucial role in estimates of the benefits, as it will take few decades before the actual benefits can be observed. In these studies cost was measured as follow-up and treatment procedure of cervical cancer and genital warts, while benefits were considered as reduced morbidity and mortality.
The mathematical models show that in countries with established cervical cancer screening programs, the addition of HPV vaccination is most likely to be cost effective. The benefits are greatly increased if the age of initial screening is increased and frequency of screening is decreased. The benefits in terms of monetary funds associated with treatment of cervical cancer and genital warts, will very within each country [32] The benefits associated with vaccination of males is predicted to be limited to reduction of cervical morbidity and is most likely not cost effective [33,34].

One recent study has looked at the potential cost-effectiveness of HPV vaccination programs in Canada. The conclusions from this study indicate that vaccinating young adolescent girls against HPV will most likely be cost effective, as long as screening programs are also in place [35]. The current available vaccines cover only four out of several oncogenic HPV types, thus the vaccination can not yet replace screening in high income countries. The continuation of screening programs will be necessary to protect individuals that have not been vaccinated [34].

Another statistical United States based study has shown that the HPV vaccination programs have a potential to be cost-effective if vaccination is combined with frequent screening for cervical cancer. Screening twice a year with an initial onset at the age of 24, along with vaccination at an adolescent age has been illustrated to be most cost-effective [36]. Another mathematical model study has confirmed the findings of these two studies, stating that vaccination is most cost-effective in women 12 to 24 years of age, undergoing regular medical checkups [37]

CONCLUSION

HPV infection is one of the most common sexually transmitted diseases among the youth today. It is a main cause of genital warts as well as development of cervical cancer in later stages in life. Treatment of cervical cancer has long been a burden in all societies, specially of those in underdeveloped nations. Current quadrivalent HPV vaccine has been shown to be efficient and safe in clinical trials, as well it has superiority over monovalent and bivalent HPV vaccines. Data obtained from clinical trials was used to evaluate safety, effectiveness and economical value of the proposed HPV vaccination. These randomized and placebo controlled trials were carried out on a large scale in various centers worldwide. Government authorities in each country have evaluated data from these trials to assess possible benefits of implementation of vaccination programs at the national level.

The following recommendations for the successful HPV vaccination program at the national level need to be assessed;

- Screening procedures for HPV such as Pap smear should be done, regardless of vaccination.
- In most countries, the target population for HPV vaccination is likely to be young adolescent females 9–13 years of age.
- It is also likely that in many countries there will be a need for older adolescents and adults to be included as part of a "catch-up" vaccination campaign.
- Further clinical studies will be needed to asses the possibility of vaccinating males and establishing herd immunity.
- Due to many new vaccines being developed each day and competing healthcare priorities, HPV vaccines will be subject to tough competition for receiving funding and implementation of policy by the government. Results from the future cost-benefit analyses will be needed to further asses benefits of the vaccination programs and help governments make the right decisions.

- Further studies are needed to test possibility of concomitant vaccination with other diseases, in order to implement HPV vaccination as part of school vaccination programs.
- Education of the public and health professionals is needed for implementing accurate vaccination strategies.

The successful introduction of HPV vaccination programs will require several interlinked components, and it will clearly be a challenge to make certain that all of these components come together in a correct way. Data on cost-benefit analyses are still being evaluated, and it will take couple of decades before any benefit from vaccination programs can be seen. However, countries such as Canada that have implemented national HPV vaccination programs will provide crucial information regarding success of these programs for those countries that have not yet introduced them.

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APPENDIX I – ABBREVIATIONS

AIS	cervical adenocarcinoma
AE	adverse event
CIN	cervical intraepithelial neoplasia
CI	confidence interval
cRIA	competitive radioimmune assay
EGLs	external genital legions
EMEA	European Agency for the Evaluation of Medicinal Products
FUTURE	females united to unilaterally reduce endo/ectocervical disease
FDA	food and drug administration
GMT	geometric mean titer
HBV	hepatitis B vaccine
HPV	human papilommavirus
HR	high risk
IFN	interferon
JRPP	juvenile respiratory papillomatosis
kbp	kilo base pairs
LR	low risk
mMU/ml	milli-Merck unit per milliliter
mcg	mili centigram
PPI	per protocol immunogenicity
PPP	per protocol population

RRP	recurrent respiratory papillomatosis
VaIN	vaginal intraepithelial neoplasia
VIA	visual inspection test with acetic acid
VIN	vulvar intraepithelial neoplasia
VILI	visual inspection test with Lugol's iodine
VLP	virus like particles
WHO	World Health Organization

APPENDIX II - LIST OF TABLES

ABSTRACT

Quadrivalent Human Papillomavirus Vaccine- Evaluation of clinical effectiveness and national vaccine programs

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SUMMARY

QUADRIVALENT HPV VACCINE- EVALUATION OF CLINICAL EFFECTIVENESS AND NATIONAL VACCINE PROGRAMS

Background: Human papillomavirus types 6, 11,16 and 18 cause majority of genital warts and cervical cancer. Recent manufacture of quadrivalent HPV vaccine is an intent to prevent and reduce morbidity and mortality.

Aim of Study: The aim of this summarized study is the evaluation of effectiveness, safety and the economical value of quadrivalent HPV 6/11/16/18 vaccine (Gardasil/Silgard) manufactured by Merck co. Recommendations for successful national vaccination programs.

Methods: The study was performed using bibliographical investigation of various scientific databases, government publications and manufacturer's publications.

Results: Current quadrivalent HPV vaccine has been shown to be efficient and safe in clinical trials. Several components are needed to be assessed for successful vaccination programs including: government will and financial support, education of the public, vaccination cost and supply, need of booster dose, identification of the target group, cost benefit and cost-effectiveness analyses. Countries with existing national vaccination programs will be a model for those who have not implemented vaccination programs at the national level.

Conclusion: Quadrivalent HPV vaccine is still in its early stages of implementation at the national level, currently providing added prevention benefits. However, future studies on effectiveness of the vaccination programs will be a focus in aim of maximizing benefits.