Public Health Implications
of Human Papilloma Virus Vaccination:
With Reference to the German Situation

Master Thesis

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by

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"All scientific knowledge is incomplete – whether it be obeservational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us the freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time."

Sir Bradford Hill

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1. Abstract

Background: Cervical cancer constitutes a major burden of disease with nearly 500,000 new cases each year, 83% of which are seen in the developing world. More than 6500 cases of invasive cervical cancer are diagnosed in Germany annually with the mean age at diagnosis being 52 years. It constitutes 3.4% of all cancers in women, yet it accounts for 25% of cancers in the 25 –35 year age group. Human Papillomavirus (HPV) infection which is the most common sexually transmitted infection has been proposed as the first ever necessary cause of a human cancer associated with more than 99.7% of cervical cancers. Of the more than 130 genotypes identified 15 types have been labelled as high risk types. In view of the promising research results of prophylactic HPV VLP vaccines, this review aims to explore the public health potential which the introduction of such a prophylactic vaccine could have in the German context and to identify the influencing factors.

Method: A comprehensive literature search was carried out using online databases, reference lists of relevant articles and abstracts of recent conferences. Data on incidence, prevalence and association of HPV infection and cervical cancer was collected. Information on Vaccine efficacy and safety, duration of protective immunity and cost-effectiveness of a HPV vaccination was searched for. In addition information on the ideal age of vaccination, public knowledge and perception and vaccine coverage in Germany was gathered.

Results: The oncogenic HPV types 16 and 18 are associated with 71.5% of cervical cancers in Europe. Several randomized control vaccine efficacy trials have demonstrated an efficacy of 90% - 100% in preventing persistent infection and a 100% efficacy in preventing precancerous cervical lesions over a follow-up period of 40 months. The vaccines were found to be safe, inducing seroconversion in 99 – 100% of vaccinees. The duration of protective immunity and the minimum serum L1 antibody levels required to give protection have not yet been determined. Model calculations reveal that a vaccination programm targeting 12 year old girls before they become sexually active, is a cost effective intervention leading to a substantial populations benefits.

Discussion: Impact of HPV vaccination on cervical cancer incidence at population level will depend on the length of induced immunity, number and interval of booster doses required, vaccine coverage of population at risk, societal acceptance and costs involved. If results from the large scale trials are similar to the phase II trials and model calculations hold true, given a high vaccine coverage a HPV vaccination would have a profound effect in reducing the burden of cervical disease in Germany.

Key words: Human Papillomavirus vaccination, Public Health, Germany, Cervical cancer prevention

2. Background

The **viral etiology** of cancers is gaining increasing importance. It is estimated that 10 – 15% of cancers are associated with viral infections. In 1964 the Epstein Barr virus was isolated from lymphoma cells of a Burkitt's lymphoma and it has been associated with cancers of lymphoid origin. The chronic carrier state of Hepatitis B and particularly of Hepatitis C predisposes to hepatocellular carcinoma. The association of Human Papilloma virus with cervical cancer came up in the early 80's, enormous research since has provided the scientific evidence for this relation.

2.1 Incidence of cervical cancer

Cervical cancer occupies the seventh position among all cancers yet it is the second most common cancer among women worldwide. An estimated 493,000 incident cases and 274,000 deaths were attributed to cervical cancer in the year 2002. 83% of these cases occur in developing countries where it accounts for upto 15% of cancers in females in contrast to 3.6% in developed countries.[1]

The age standardized incidence rates vary considerably among different world regions and countries. Low rates are observed in Western Asia 5.8/100,000 and China 6.8/100,000 while highest incidence rates of upto 43/100,000 are seen in East and West African countries and high rates between 30.6 – 32.6/100,000 are observed in the Caribbean and Central American region.[1]

In Europe the incidence rates vary between 9/100,000 in Northern Europe and 14.5/100,000 in Eastern Europe.[1] As seen in Fig.1 the lowest incidence rates of cervical cancer in the European Union are seen in Finnland, Luxemburg and Spain.

Comparison of cervical cancer incidence in the EU
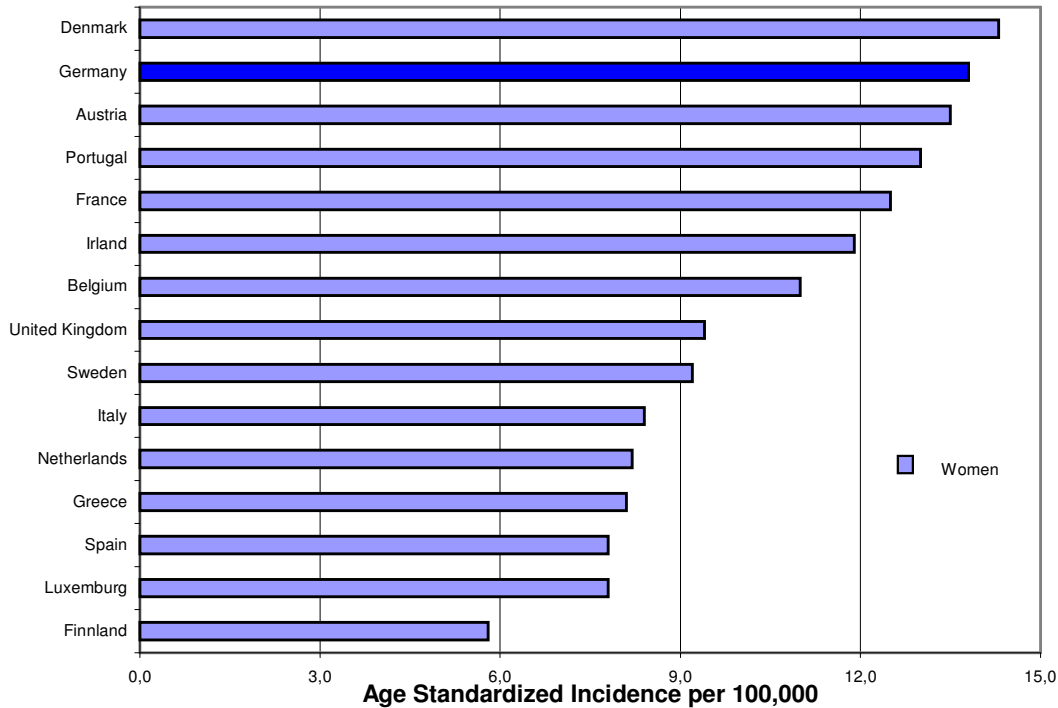
Figure 1: Age standardized incidence of cervical cancer in the European Union

Taken from: EUCAN 98, Estimations for Germany by the Robert Koch Institute 1998 [2]

2.1.1 Cervical cancer incidence and mortality in Germany

In Germany 6,580 new cases and 1,900 deaths were attributed to cervical cancer in the year 2000. This accounts for 3.4% of cancers and 1.9% of cancer associated deaths in females. As seen in Fig.1 Germany is only preceded by Denmark in the European Union in its frequency of cervical cancer incidence. The age standardised incidence is estimated at 13.8 / 100,000 persons/year for the whole of Germany.[2] The age distribution is different from most other malignancies in that 2/3 of cervical cancers are diagnosed before the age of 60 years (Table1).The mean age of incidence being 52 years.[2]

There has been a dramatic reduction in the incidence and mortality of cervical cancer since the early 70's. From 1980 – 1995 the incidence of invasive cervical cancer in Germany reduced by 40%.[3] One of the major factors responsible for this trend in high income countries was the introduction of organised screening programs, in addition to a reduction in population fertility and improved diet. The 5 year survival rate has not improved significantly being around 65% for all stages of invasive cervical cancer.[2] Prior to these organised

screening activities the incidence rates in Europe, North America and Australia were comparable to those in the developing countries today.[1]

Statistical Overview on Cervical Cancer in Germany			
	Cases	**% of all cancers**	**Year**
Incidence of Cervical Cancer	6588	3.4%	2000
Incident cases below 60 yrs	4515		
Crude incidence rate	15.6/100,000		
Age Standardized incidence rate	13.8/100.000		
Age groups	**Incidence /100,000**		
below 45 yrs.	11.5		
45 - 60 yrs.	23.8		
60 - 75 yrs.	16.4		
75 yrs. and older	22.4		
Mean Age of incidence	52 years		
	Cases	**% of all cancer related deaths**	
Cervical Cancer Mortality	1882	1.9%	2000
Mortality below 60 yrs. of age	774		
Age Standardized Mortality rate	4.5/100,000		
Age groups	**Mortality /100,000**		
below 45 yrs.	1.3		
45 - 60 yrs.	5.7		
60 - 75 yrs.	7.7		
75 yrs. and older	14.3		
5 year survival rate of all stages combined	65%		

Table 1: Cervical cancer incidence and mortality rates in Germany

Adapted from: Arbeitsgemeinschaft Bevoelkerungsbezogener Krebsregister in Deutschland

and the Robert Koch Institut. 4th Edition Saarbruecken 2004 [2]

http://www.rki.de/Krebs

2.2   Human Papilla Virus

2.2.1   Epidemiology of Human PapillomaVirus Infection

HPV infections are among the most common sexually transmitted infections, estimates of exposure range between 15 – 20 % with a life time risk of being infected of 75% – 85% for many european countries.[4,5] The infection is asymptomatic in most cases and hence not noticed. Highest exposure to HPV occurs soon after initiation of sexual activity. Assessment of virgins after their sexual debut showed that levels of HPV infection were 40% after 24 months and rose to 70% by 56 months.[6] The cross sectional prevalence reduces to 2-8% in most populations in the age group of 30 and above.[44] The fact that prevalence falls rapidly is most likely due to the development of immunity which clears the infection.[7] As seen in Fig.2 the peak age of acquiring an HPV infection is before the age of 25 yrs. while the incidence of cervical cancer rises much later.
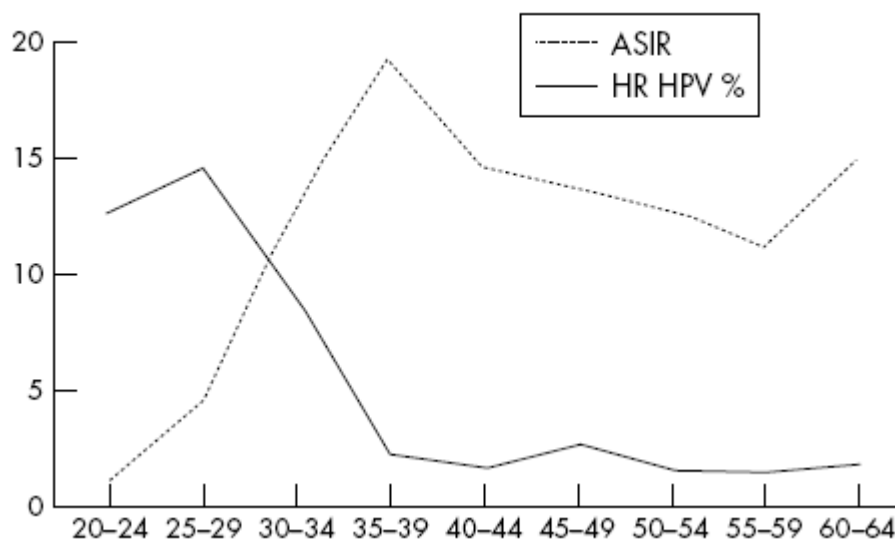
Figure 2: Age specific prevalence of HR-HPV DNA (HR-HPV%) and Age specific incidence (x 10^5) (ASIR) of cervical cancer in 3700 women entering a screening programm in Netherlands [16]

Follow-up studies investigating viral persistence have shown that the median duration of infection for high risk HPV types is 8 – 13.5 months while that of low risk HPV types is shorter ranging between 4.8 – 8.2 months.[8,9] These durations are estimations as it is difficult to establish the precise time of first exposure. The longest persistence occurs with HPV

type16. It is estimated that about 2% of those infected with the HPV actually develop invasive cervical cancer.[10]

15% – 30% of women who are infected with a high risk type of HPV and have a cyto-morphologically normal test, will develop a CIN 2 or CIN3 lesion within 4 yrs following identification of infection.[11]

Women infected with a HR-HPV type are estimated to have a relative risk 10 for developing a dysplastic or precancerous cervical lesion.[12,13] It ranges from 7.8 – 20.9 in different studies assessing the progression from HPV infection to CIN 2 – 3. [44]

As more sensitive HPV DNA detection methods (GP5+/6+, PGMY09/11) are being employed today, recent studies have demonstrated that HPV DNA can be detected in 99.7% of all cervical cancer specimens with types 16, 18, 45 and 31 being the most frequent.[14]

2.2.2   HPV Structure and Oncogenesis

Unlike bacterias, viruses are not cells and hence incapable of reproducing independently. They comprise of an inner core containing DNA or RNA and a protective protein coat, and are dependent on host cells for replication.

The human papilloma virus (HPV) is a non enveloped double stranded DNA virus comprising of a protein capsid (made of 72 capsomers) which contains the viral genome. The capsomers are made up of two structural proteins, the L1 protein forming approx. 80% of the capsid and L2 forming 20%.
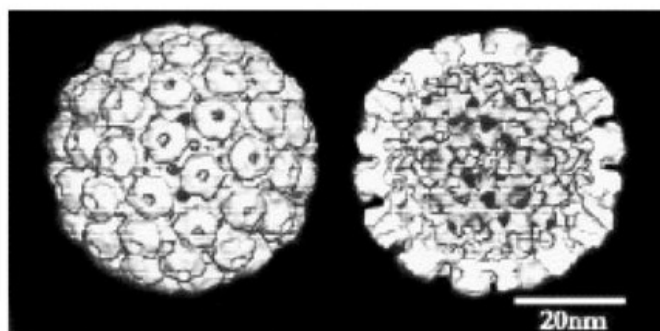

Figure 3: Capsid model of HPV-16

Source: (www.uchsc.edu./sm/molbiol/rgarcea.html)

The HPV viral genome can be divided into 3 regions, the long control region, the region which codes for the early proteins (E1 – E8) and the region coding for the late capsid proteins (L1 and L2). Of the proteins coded by the early genes, the proteins E6 and E7 are the most important oncogenic proteins involved in tumorigenesis. p53 and pRB are tumor supressor proteins (in human cells) whose function is suppressed by the binding of E6 and E7 respectively thus leading to transformation and immortalization of the host cell.[15]
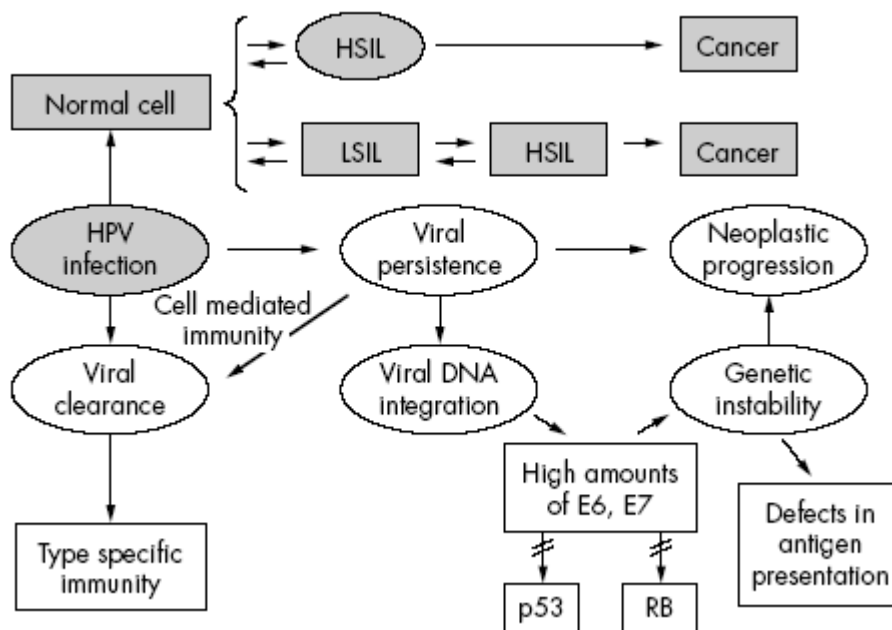
Figure 4: Mechanism of HPV Carcinogenesis

This diagram is a schematic representation of some of the important steps involved in the transition from HPV infection to cervical cancer or to development of immunity. Whereas transient infections are largely subclinical, progression is closely related to the persistence of viral DNA.[16]

In most low-grade cervical cancer precursor lesions, HPV DNA exists in episomal form, while in most high-grade precursor lesions, 75% of HPV16- and almost all HPV18-associated carcinomas, the HPV genome becomes physically integrated into the host chromosomal DNA which could result in uncontrolled cell proliferation.[17]

The structure of the genome is similar for all HPV viruses yet the low risk HPV types have a much lower potential of initiating an oncogenic process owing to the functional difference that exists between the E6 and E7 proteins of the high risk and low risk types. The low risk

HPV (LR-HPV) types 6 and 11 for instance do not cause the degradation of the p53 tumor supressor protein.[18]

2.2.3 Life Cycle of the Human Papilloma Virus
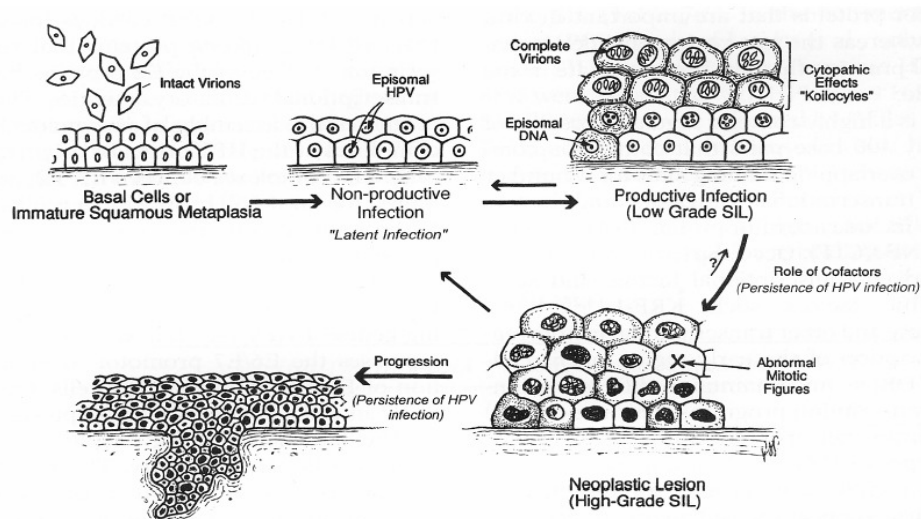
Figure 5 :   Lifecycle of the HPV in the host cell

The HPV shows a distinct epitheliotropic nature. The intact virions enter through micro-abrasions in the epithelium and infect the immature squamous epithelial cells of the deep basal layer. Within these cells the virus can exist in the non-productive or the productive phase. In the non-productive or latent phase of controlled replication a small number of HPV genomes (50 – 100) are present in free (extra-chromosomal) from in the nucleus of the basal cells. As the basal cells divide some cells stay within the basal layer contributing to a reservoir of viral DNA while some epithelial cells might enter into the productive phase i.e. towards cell maturation. In this productive phase viral DNA replication occurs independent of the host cells and a large amount of infectious virions are produced. This replication occurs in the intermediate and superficial layers of the epithelium. As the viraly infected cells mature they move to the surface and shed mature infectious virions.

2.2.4 HPV Types

The HPV has been broadly classified into cutaneous types seen predominantly in skin warts and genital types primarily infecting the mucosal epithelium of the anogenital area.

More than 130 different genotypes of the Human Papilloma Virus have been identified. 30 - 40 types are known to infect the anogenital tract. The genotypes are classified on the basis of a ≥ 10% difference in the DNA sequence with respect to previously established strains.[44] The genital HPV types have been subdivided into Low risk (LR-HPV) types which cause mainly benign lesions like genital warts e.g. condylomata accuminatum and High risk (HR-HPV) types which are mainly associated with cervical intraepithelial neoplasia and cervical cancer.[19]

Human Pailloma virus infection has also been associated with other mucosalepithelial tumors involving the vulva, vagina, anal canal, perianal skin, penis and some oropharyngeal cancers.

2.2.5 HPV Classification on the basis of Oncogenic Potential

About 15 HPV types are involved in over 95% of cervical cancer cases, these types are labelled as HR-HPV.[16,19] HPV-16 and HPV-18 are the most common types, HPV-16 being involved in approx. 50% - 60% and HPV-18 in approx.10% - 20% of cervical cancers.[14,16] In 1995 the International Agency for Research on Cancer (IARC) on the basis of several case control studies classified Types 16 and 18 as human carcinogens. Since then additional case control studies have revealed that types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82 should also be considered as carcinogenic or HR- HPV types. 12 genotypes have been classified as Low risk. Types 6, 11, 40, 42, 43, 44 being the most common are mainly detected in genital warts, flat condylomas and low grade intraepithelial neoplasia. This information is essential for HPV prevention and screening programs.[19]

2.2.6 Strength of Association

The odds for developing cervical cancer only in the presence of HPV DNA ranges from 50 – 100 fold which is much higher than the ORs for other known cancers and their risk factors as seen in Table 2 . ORs for specific associations like HPV 16 and squamous cell carcinoma and HPV 18 and cervical adenocarcinoma range between 100 – 900. These estimates lead to attributable fractions of over 95%.[20,16]

Association	Relative Risk / Odds Ratio	Attributable Fraction %
Cigarette smoking and lung cancer	10	80%
HCV and liver cancer in Italy	20	40%
HBsAg and liver cancer in Greece	50	60%
HPV-DNA and cervical cancer in Bangkok	100	90%
HR-HPV-DNA and cervical cancer in Costa Rica		80%
HPV-DNA-18 and cervical adenocarcinoma in Philippines	>500	99%

Table 2: Selected examples of the strength of association between risk factor and human cancer

Source: Adapted from Bosch et al. The causal relation between human papillomavirus and cervical cancer [16]

Systematic review of the causality criteria strongly indicates that the association of HPV and cervical cancer is causal in nature. This association is strong, consistent, specific and universal. HPV infection precedes preinvasive disease and the evidence of biologic plausibility is persuasive.[16]

HPV has been proposed as the first ever necessary cause of a human cancer which implies that cervical cancer will not occur in the absence of the persistent presence of HPV infection.[16]

2.2.7   Methods of HPV detection

The development of new testing methods for HPV DNA detection in the 1980's led to the establishment of its etiologic role in cervical carcinogenesis. With the advancement in technology the sensitivity of the tests improved so that the number of cervical cancer cases where HPV DNA was detected greatly increased. The presence of human papillomavirus can be demonstrated by detecting HPV-DNA in the cell smear or tissue, or by the presence of

HPV proteins in the tissue. To a limited extent antibodies against HPV can be measured in the serum.[21]

It is not possible to grow HPV in cell cultures hence molecular-biological and DNA amplification techniques have to be applied to detect and differentiate the different HPV types. The polymerase chain reaction (PCR) technique which amplifies the HPV-DNA is a highly sensitive detection method and false positive results are not an issue. The hybrid capture (HCI & HCII) methods which amplify the HPV-DNA signal is another highly sensitive technique which has been approved by the US FDA and is mainly used now.

Figure 6: Development of HPV DNA detection tests and their sensitivity in the past two decades

Source: Taken from Bosch et al. The causal relation between human papillomavirus and cervical cancer [16]

2.3   Precancerous Cervical Lesions

2.3.1   Cervical Anatomy and Histopathology of Cervical Intraepithelial Neoplasia

The uterine cervix is about 2-3 cms long, the portion protruding into the vagina is lined by non-keratinizing squamous epithelium, at the external cervical os the epithelium changes to simple columnar which lines the endocervical canal. This transition zone also known as the squamocolumnar junction during puberty under the influence of hormones shifts towards the exocervix, this makes it more accessible for screening tests, while it retracts into the endocervical canal after menopause making an early diagnosis more difficult at that stage.[22]

The squamocolumnar junction (transition zone) is particularly vulnerable to dysplastic changes, 90% of the squamous epithelial dysplasias develop in this region while about 10% occur in the endocervical canal.[23]

The invasive cervical cancer does not develop suddenly, rather it is preceded by precancerous lesions known as cervical intraepithelial neoplasia (CIN). These lesions may persist for 1 – 3 decades before a frankly invasive cancer develops. 75% - 85% of cervical cancers are squamous cell carcinomas in origin and 15% - 25% are adenocarcinomas.

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2.3.2 Pap Screening Method and Sensitivity

The pap test named after Dr. George Papinicolaou (1928) is a cytological test which is the first step in screening for cervical cancer. It classifies the lesion as normal, precancerous or cancer depending on the epithelial layers the atypical cervical cells originate from. The fact that invasive cervical cancer is preceded by precancerous lesions for considerable time periods makes such a cytologic screening test a useful means of prevention.

A smear is obtained by scraping cells under vision from the exocervix at the squamo-columnar junction and from the endocervical canal with the help of a spatula, cotton swab or a cyto brush. The quality and reliability of the result is dependent on the technique employed to obtain the sample, the method and accuracy with which the slide is prepared and the expertise of the cytotechnician.

The Pap tests high false negative rate is its most critical limitation. According to a recent meta-analysis the average sensitivity of Pap cytology to detect CIN or invasive cervical cancer was 51% while the average specificity was around 98%.[24,7] This limitation is overcome to some extent by the repeated annual screening test which may pick up lesions missed previously. About one-third of false negative diagnosis are attributable to false slide interpretation and two-thirds to poor sample collection.[7]

In Germany organised pap screening was introduced in 1971. Starting from the age of 20yrs. all women are entitled to a yearly cervical smear test. According to the national health survey the annual utilization of screening facilities (early detection of breast and cervical cancer) by eligible women is 36.5% while the National Association of Statutory Health Insurance Physicians estimated it to be around 51% in 1997.[45,46]

2.3.3 Cervical Intraepithelial Neoplasia and Invasive Cervical Cancer

CIN can also be defined as a histologic classification which on the basis of the degree of cellular atypia (dysplasia) and abnormalities in cell division and cell structure defines the extent of the precancerous lesion.

In CIN I and CIN II the immature cells are seen in the inner third or inner 2/3 of the epithelium respectively while in CIN III or carcinoma in situ (CIS) the entire thickness of the epithelium upto the surface is involved but it does not cross the basement membrane. 60% of

CIN1 lesions regress spontaneously while about 10% progress to CIN 2. A meta-analysis of the natural history of cervical dysplasia estimated that 22% of CIN 2 lesions progress to CIN 3 without treatment while in the case of CIN 3 and CIS 70 – 100% progress to cancer if left untreated and hence women with CIN 3 are at substantial risk of developing invasive cancer.[25,22]

The diagnosis specially of low grade precancerous lesions has been difficult and led during the last 20 years to the development of four different cytological/histological classification systems.[21]

Classification systems of Cervical Cytology/Histology

PAP	DYSPLASIA WHO/ISGYP	CIN	BETHESDA 2001
I	Normal	-	Normal and variants
II	Reactive chan ges Atypia, Koilocytosis (condylomatous change)	-	Reactive changes
III	-	-	ASCUS/AGUS
III d	Mild	I	Low grade SIL
-	Moderate	II	High grade SIL
IV a	Severe	III	High grade SIL
IV b	CIS	III	High grade SIL
V	Carcinoma	Carcinoma	Carcinoma Microinvasion (<3 mm) Frankly invasive (>3mm)

Table 3: Comparison of Classification systems

ISGYP : International Society of Gyneacological Pathologists

CIN   : Cervical Intraepithelial Neoplasia

SIL   : Squamous intraepithelial lesion

CIS   : Carcinom in situ

ASCUS : atypical squamus cells of undetermined significance

AGUS   : atypica glandular cells of undetermined significance

The Bethesda system is more frequently used in the United States. In Germany the WHO/ISGYP and the CIN classification systems are commonly used to describe the grade of neoplasia.

2.3.4 Epidemiology of Cervical Intraepithelial Neoplasia

CIN is predominantly a disease of women in their reproductive years, with a large population impact. The prevalence of CIN has increased during the last decades, especially among younger women. The peak incidence is seen in the 25-29 year old group and decreases with age thereafter.[26]
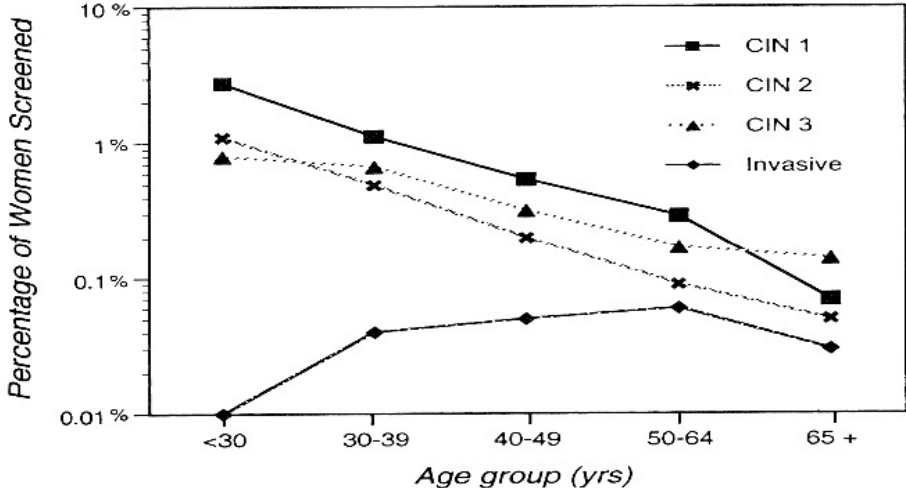
Figure 7: Impact of age on the prevalence of biopsy-confirmed cervical lesions

Source: Data from the National Breast and Cervical Cancer Early Detection Program in US demonstrates a reduction in the prevalence of both low-grade CIN and high-grade CIN with increasing age. The prevalence of invasive cervical cancer increase until the age 64 years.[27]

The number of diagnosed precancerous cervical lesions (dysplasias, cervical intraepithelial neoplasia (CIN), and carcinoma in situ (CIS) is 30 - 100 fold higher then the actual incidence of cervical cancer. For Germany the incidence of precancerous lesions of the cervix is estimated to be around 300,000/year.[21]

2.3.5 Management of CIN

Standard treatment procedures depending on the degree of lesion include excision techniques like cold knife conization or loop electrosurgical excision which are associated with post-operative bleeding. Other less invasive procedures are cryo-therapy and laser ablation with the disadvantage that they do not provide pathological specimens that can be tested. In some cases a hysterectomy may be indicated.

These procedures have efficacy rates of approximately 90% but are associated with morbidity. They cause destruction of the cervical stroma, which may lead to scar stricture

with increased risk of infertility and necessity of subsequent caesarean section or, adversely, cervical incompetence with premature deliveries and low-birth-weight babies. In few cases the CIN can relapse as surgical treatments remove only the dysplastic tissue, leaving normal-appearing tissue which maybe HPV-infected untreated.[28]

2.4   Genital Warts

Condyloma acuminatum also known as genital warts are papillomatous proliferative lesions of the squamous epithelium of the vulva, vagina or cervix caused by the human papilloma virus. The low risk HPV types 6 and 11 cause over 90% of these genital warts, which are mostly benign.

Estimates indicate that 1% of the adult population worldwide have genital warts.[29]

In the UK between 1972 and 2004 the number of all genital warts diagnosed increased 8 fold in men and 11 fold in women. These rises may reflect not only an increased incidence of infection but also greater public awareness and improved diagnostic sensitivity. The peak age of incidence for females was between 16 – 19 yrs with 30% of cases occurring below the age of 20 yrs.[30]

The US Institute of Medicine in 1994 estimated the total annual costs (direct and indirect) of HPV related diseases excluding HPV associated cancer to be $3827 million.[31,44]

The vast majority of HPV associated warts cause little physical discomfort but in some cases irritation and soreness are reported in addition to the fact that genital warts are psychologically distressing for many people. The lesions are much more profuse in patients who are pregnant, diabetic, receiving oral contraceptives or immunosuppresent therapy.

Genital warts in pregnancy bear the risk that the virus may be passed on to the infant at birth. This can very rarely cause laryngeal papillomatosis, pharyngeal or anogenital warts which my obstruct the airways and require repeated surgery. Some large warts may be an indication for delivery by caesarean section.[32]

10 – 20% of condyloma accuminatum resolve spontaneously. Treatment choice depends on the morphology, size and area affected, it includes the application of chemicals like podophyllotoxin a cytotoxic agent, imiquimoid cream an immune response modifier or Trichloroacetic acid. An alternate option are ablative procedures including cryosurgery, surgical excision, electrocautery or laser therapy. All these treatments may eradicate the warts yet they do not eliminate the virus and hence recurrence is seen also depending on factors like host immunity, cigarette smoking etc.

2.5 Risk Factors for HPV associated Cervical disease

- **Age** (as seen in Tab. 1) seems to show a certain trend, cervical cancer is seldom seen in women below 20 yrs. and increases with age with a peak incidence between the age of 40 –60 yrs. In contrast the peak incidence of genital HPV infection is between the age of 20 – 24 yrs and then shows a decreasing trend with increasing age. The reason for this age dependence seems to be the development of immunity, hormonal changes and the decreasing exposition with age. The long latency phase is probably the answer for the 20 – 30 yrs gap between infection and development of cancer.[21]
- **Multiple and changing sexual partners** bears an increased risk of developing a CIN or invasive cancer as seen in an analysis of 10 case-control studies. The relative risk lies between RR: 1.7 and 9.0. When controlled for HPV infection the RR decreases.[21]
- **Initiation of sexual activity** at a young age (below 16 yrs) carries a RR of 1.1 – 16.1 for developing cervical neoplasia, this is probably due to the cervical epithelium being more vulnerable to the cell transforming changes by the human papilloma virus and it may also be the early age at infection. The RR reduces significantly when controlled for HPV infection.[21]
- **Low socio-economic status** is associated with cervical cancer yet it is difficult to label it as an independent factor. Decreased utilization of screening facilities and other risk factors are more frequently seen in women belonging to a lower socio-economic status.[21]

- **Multiparity,** In the IARC multicentre study, HPV positive women who reported seven or more full term pregnancies had a fourfold increased risk of cervical cancer compared with similar HPV positive women who were nulliparous (OR, 3.8; 95% CI, 2.7 to 5.5).[16]

- **Genitaltract infections** like Herpes genitalis or Chlamydia predispose to cervical cancer yet this effect cannot be seen when controlled for HPV infection.

- **Smoking** and cervical cancer of squamous cell type revealed a positive correlation in 14 case control studies, yet this effect is not independent of a HPV infection.[21] Nicotine and its by-products concentrate in the cervical mucus and decrease the ability of the cell mediated immune system to protect the cells against infection.[33]

- **Oral contraceptive** (OCPs) use seems to increase the risk of developing CIN and cervical cancer (RR: 1.1 – 3.2) , yet in 12 of 14 case control studies no dose – effect relation could be seen. 2 separate studies demonstrated a higher risk of developing an invasive cervical cancer for HR-HPV positive women who use OCPs, this maybe due to the increased transformation in HPV infected cells.[21]

- **Genetic predisposition** apparently plays a role as shown from the data analysis of the Swedish National cancer registry demonstrating a higher relative risk for developing cervical cancer in family members of cervical cancer patients, for biologic mothers compared to control cases, a RR of 1.83 (CI: 1.77 – 1.88) and for real sisters a RR of 1.93 (CI: 1.85 – 2.01) [12]

- **Immunosuppression** by leading to a deficiency of cell mediated immunity increase the likelihood of HPV persistence and disease expression, in patients receiving corticosteroids or chemotherapy or immunosuppresent drugs for e.g. transplant recipients or people suffering from diabetes or HIV.[21]

2.6   Immunology

In the majority of cases an infection with the human papillomavirus is prevented by the immune system.[34] The significance of an adequate immune response in limiting the progression of HPV infection to cervical cancer is supported by the fact that there is a higher incidence of both HPV infection as well as CIN , CIN recurrence and cervical cancer in immunocompromised patients.[44]

The HPV resides in the cells of the basal epithelial layers, where there is little replication and exposure of the HPV antigen allowing the virus to escape the immune system. The HPV infection does not cause viremia and has no systemic manifestations. The virus does not kill

the infected cell and consequently no local inflammatory response is generated either. The virus is able to persist in the host cell for long time periods due to its low immunogenecity which is also seen by the weak and delayed immune response both antibody and cell mediated demonstrated in normal individuals in case of an HPV infection.[35,32]

It is only when mature host cells with intact virions reach the surface and are shed that the viral antigens become exposed to the host immune system and could generate an antibody response. [44]

Humoral immunity is mediated through B-lymphocytes which produce immunoglobulins (neutralizing antibodies) which by binding to a particular antigen lead to the destruction of extracellular pathogens. The capsid proteins which induce a significant immune response when injected systemically, do not stimulate the same response in a natural (local) infection owing to the lack of access of the immune system to these proteins (intracellular). Antibodies against the early E6 and E7 proteins are primarily found in patients suffering from CIN III lesions and HPV associated tumors.[36]

Intracellular pathogens are dealt with by the cell mediated immune system which plays a critical role in destroying virally infected cells. Cytotoxic T-lymphocytes (CTLs) recognize the foreign peptide antigens presented on the surface of the infected cells by the human leucocyte antigens and induce an immune response. CTLs have been observed in cervical tumors as well as in regressing condylomas. Hence HPV infection, development of CIN and cervical neoplasia are considered to be associated with impaired cell-mediated immunity rather then failure of humoral immunity

According to one study women seem to be protected against re-infection with the same HPV type but not against other HPV types even those closely related, hence the likelihood of cross protection appears to be little.[37,44]

2.7 Preventing Cervical Cancer

Condom use may not be as effective in preventing HPV infection as it is in preventing other STDs. HPV apart from being present in the mucosal epithelium of the vagina, cervix, urethra and anus is also present in the skin cells of the pubic area and may hence be transmitted by contact with infected skin cells.[38] The use of condoms by males does reduce the virus load and can still offer substantial protection.[39,44] Male circumcision also protects males from becoming HPV carriers and hence transmitting the infection to the sexual partners.[40,44]

Pap screening is the main method of secondary prevention used. The causal connection between HPV infection and cervical neoplasia allows HPV DNA to be used as a tumor marker to improve the accuracy of the Pap test. Detection of oncogenic HPV DNA is also used as a secondary test (triage test) for minimally abnormal or unequivocal cytology results.[7]
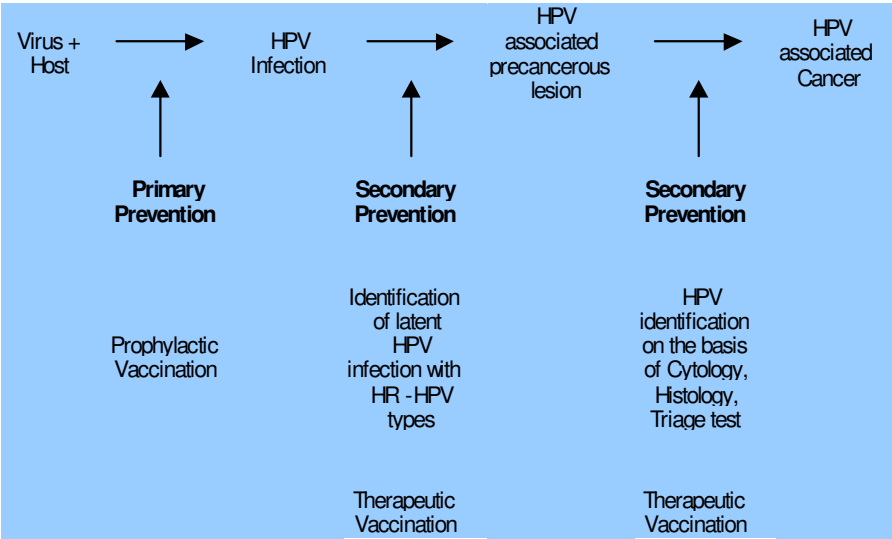
Figure 8: Primary and Secondary Prevention Methods

Source: Taken from Schneider et al. Epidemiologie, Aetiologie und Praevention des Zervixkarzinoms [21]

2.7.1 Prevention through Vaccination

As the human papillomavirus infection plays a primary etiologic role in the development of cervical cancer, it led to extensive research with the aim to use vaccination as a tool for cancer prevention and treatment. During the past 2 decades research efforts have led to the development of two vaccine strategies. The classical prophylactic (preventive) vaccine to which all the currently licensed vaccines belong and a new group of therapeutic vaccines that induce regression of an already established infection or its sequel.

2.7.1.1   Prophylactic Vaccines

The aim of a prophylactic vaccine is to prevent an infection. The capsid proteins are the only antigens accessible for a neutralizing antibody to prevent infection. The late structural protein 'L1' which forms a major part of the HPV capsid, has high antigenic properties.

HPV infection may be prevented via virus neutralizing antibodies produced by the B-lymphocytes in response to the L1 virus like particle (VLP) of the specific HR HPV types. Protection against sexual transmission of HPV requires neutralizing antibodies acting locally on the mucosal surfaces. Specific serum IgG and secretory IgA antibodies may enter the genital tract by exudation on the mucosal surface for e.g. mucosa of the cervix, where they could come in contact with the virus thereby inactivating it thus preventing its entry into the basal cells.

This VLP which is a subunit vaccine could be an ideal vaccine as it neither contains the viral DNA nor any oncogenic proteins. The vaccine against Hepatitis B is the first example of a VLP vaccine.

A breakthrough was achieved when Zhou et al. in 1991 showed that HPV-16 L1 capsid protein, when expressed in a recombinant system, formed virus-like particles (VLPs) that resembled native virions.[41] These L1 proteins have the property of assembling themselves into virus like particles which resemble the viral capsid

Intramuscular vaccination of women with HPV-16 VLPs was found to induce significant antibody titers in serum and cervical secretions and sufficient antibody levels were maintained across the menstrual cycle.[42] The immunity conferred seems to be type specific i.e. only against the HPV type against which the vaccine is developed and there seems to be no cross protection against the other HPV types.

2.7.1.2   Therapeutic Vaccines

In the process of cervical tumor development there is integration of the viral DNA into the host genome with loss of virion production i.e. the late capsid proteins L1 and L2 are not expressed and hence prophylactic vaccines are ineffective. Cellular immune response appears to be the key component necessary for clearance of established HPV infections and therefore would be the main target of any therapeutic HPV vaccine.

The consistent expression of the early oncogenic proteins E6 and E7 in more then 90% of cervical cancers renders them as tumor specific antigens.[43] This raises the possibility that vaccination against the E6 and E7 proteins of the HR HPV types could generate specific

cytotoxic T-lymphocytes and thereby lead to a destruction of the infected tumor cells.[44] In contrast to prophylactic vaccines the antigen delivery (of E6, E7) and the development of an immunogenic response is much more complicated. The loss of HLA from the cell surface of the majority of cervical cancers and CIN enables tumor cells to escape the cellular immunity inspite of specific CTLs. Current therapeutic vaccine trials are less mature with respect to disease clearance yet significant therapeutic benefit has been seen in preclinical papillomavirus models.[28]

3. Introduction

The **viral etiology** of cancers is gaining increasing importance. It is estimated that 10 – 15% of cancers are associated with viral infections. The association of Human Papilloma virus with cervical cancer came up in the early 80's, enormous research since has provided the scientific evidence for this relation.

Cervical cancer occupies the seventh position among all cancers yet it is the second most common cancer among women worldwide. An estimated 493,000 incident cases and 274,000 deaths were attributed to cervical cancer in the year 2002. 83% of these cases occur in developing countries where it accounts for upto 15% of cancers in females in contrast to 3.6% in developed countries.[1]

In Germany approximately 6,580 new cases and 1,900 deaths are attributable to cervical cancer each year (data from 2000). This accounts for 3.4% of all cancers and 1.9% of cancer associated deaths in females.[2] In Europe the incidence rates vary between 9/100,000 in Northern Europe and 14.5/100,000 in Eastern Europe.[1] The age standardised incidence in Germany is estimated at 13.8 / 100,000 persons/year which is second only to Denmark among the countries of the European Union.[2] With a mean age of incidence at 52 years 2/3 of cervical cancers are diagnosed before the age of 60 years. In the 25 – 35 year age group cervical cancer accounts for 25% of diagnosed cancer cases while it decreases to <5% for the above 65 years age group.[2]

The incidence of invasive cervical cancer in Germany reduced by 40% from 1980 -1995.[3] One of the major factors responsible for this trend was the introduction of organised screening programs in 1971, in addition reduction in population fertility and improved diet may also play a role. The 5 year survival rate has not improved significantly and is around 65% for all stages of invasive cervical cancer.[2]

HPV infections are among the most common sexually transmitted infections, with an estimated prevalence of 15 – 20 % and a life time risk of being infected of 75% – 85% for many European countries.[4,5] The highest incidence of HPV infection is seen soon after initiation of sexual activity. The cross sectional prevalence reduces to 2-8% in most populations in the age group of 30 and above most likely due to the development of immunity.[7]

The human papilloma virus (HPV) is a non enveloped DNA virus surrounded by a protein capsid comprising of two types of structural proteins, L1 and L2. The viral genome produces

two important oncogenic proteins E6 and E7 which by binding to the human tumor supressor proteins p53 and pRB respectively lead to transformation and immortalization of the host cell.[15]

Of the more than 130 different HPV genotypes about 40 types are known to infect the anogenital tract. The genital HPV types have been subdivided into low risk (LR-HPV) types and high risk (HR-HPV).[19] About 15 HR-HPV types are involved in over 95% of cervical cancer cases. HPV-16 and HPV-18 are the most common HR-types, HPV-16 being involved in approx. 50% - 60% and HPV-18 in approx.10% - 20% of cervical cancers.[14,16] Less than 2% of those infected with the HPV actually develop invasive cervical cancer.[10] Women infected with a HR-HPV type are estimated to have a relative risk ranging from 7.8 – 20.9 for developing a CIN 2 or 3 lesion.[44]

12 genotypes classified as LR-types are mainly associated with benign lesions like genital warts and low grade intraepithelial neoplasia. HPV-types 6 & 11 are found in 90% of genital warts and condylomata accuminatum which afflicts about 1% of the population.[19,29]

Studies investigating viral persistence deemed as necessary for the development of neoplasia, have shown that the median duration of infection for high risk HPV types is 8 – 13.5 months, with the longest persistence seen with type 16, while that of low risk HPV types is shorter ranging between 4.8 – 8.2 months.[8,9]

More sensitive DNA detection methods (GP5+/6+, PGMY09/11) have led to HPV DNA being detected in 99.7% of all cervical cancer specimens.[14] The association between HPV DNA and cervical cancer is the strongest ever observed for human cancer with odds ratios ranging from 50 – 100 fold, in contrast the OR for cigarette smoking and lung cancer is 10 fold.[20]

HPV has been proposed as the first ever necessary cause of a human cancer which implies that cervical cancer will not occur in the absence of the persistent presence of HPV infection. This association has been shown to be strong, consistent, specific and universal. HPV infection precedes preinvasive disease and the evidence of biologic plausibility is persuasive.[16]

Invasive cervical cancer develops slowly taking 1 – 3 decades from infection to cancer. It is preceded by precancerous lesions known as cervical intraepithelial neoplasia (CIN) detected

by cytological Pap smear test and by histology. These lesions mostly develop at the squamocolumnar junction (transition zone) of the uterine cervix which is particularly vulnerable to infection with the HPV and development of dysplastic changes.

CIN predominantly affects women in their reproductive years, with a large population impact. The prevalence of CIN has increased during the last decades, especially among younger women. The peak incidence is seen in the 25-29 year old group and decreases with age thereafter.[26]

CIN is also a histologic classification which defines the extent of the precancerous lesion. While 60% of CIN1 lesions regress spontaneously, 70 – 100% of CIN3 and CIS lesions progress to cancer if left untreated.[25] CIN lesions are mainly treated by ablation and excision techniques. These therapies have an efficacy of approx. 90%, i.e. the lesions might recur requiring regular follow up and treatment is associated with morbidity.[28]

The fact that HPV is now considered as the main and causative **risk factor** for cervical cancer has led to completely new dimension on the epidemiological research front. All the proposed risk factors for cervical cancer including young age at initiation of sexual activity, multiple sexual partners, multiparity, low socio-economic status, smoking, oral contraception, genetic predisposition and immunosuppression are more likely to be cofactors rather than independent risk factors.[12]

Condom use offers only limited protection as the virus apart from being present in the mucosal epithelium of the vagina, cervix, urethra and anus is also present in the skin cells of the pubic area and may hence be transmitted by contact with infected skin cells.[38,39]

Secondary prevention through Pap screening is the main method used to date. The causal connection between HPV infection and cervical neoplasia allows HPV DNA to be used as a tumor marker specially in case of unequivocal Pap cytology results.[7] As HPV infection plays a primary etiologic role in the development of cervical cancer, extensive research over the past 2 decades led to the development of vaccination as a tool for primary prevention.

The prophylactic vaccines aim to prevent HPV infection by stimulating the immune system to produce neutralizing antibodies. The structural protein 'L1' which forms a major part of the HPV capsid are the only accessible antigens. They possess high antigenic properties and are the target of the neutralizing antibodies. The antibodies may enter the genital tract by

exudation on the mucosal surface for e.g mucosa of the cervix, where they could come in contact with the virus thereby inactivating it thus preventing its entry into the basal cells.

These L1 proteins have the property of assembling themselves into virus like particles (VLP) which resemble the viral capsid yet are devoid of viral DNA making it an ideal subunit vaccine.[41] Vaccination with HPV-16 VLPs was found to induce significant antibody titers in both animal and human tests.[42]

This review aims to explore the public health potential which the introduction of a prophylactic HPV vaccine could have in the German context as well as to identify the influencing factors that would guide future decisions of policy makers in favour or against a recommendation.

4. Methods

An intensive literature search was conducted which provided the basis for this review. Online databases including Medline, Pubmed and CancerLit were searched and relevant studies, reviews and trials identified. Search terms included 'human papilloma virus (HPV) vaccination', 'cervical cancer prevention', 'epidemiology of HPV' and 'cost benefit analysis and HPV vaccination'.

Articles upto December 2005 were considered for the review, preference was given to more recent studies. Papers written in English and German language were selected. Further relevant papers were identified from the reference lists of the retrieved articles. In addition international journals with a public health focus were hand searched.

The selected articles were studied for information on the natural history of HPV infection, the type specific distribution, peak age of incidence and the risk factors for infection. In addition information on the epidemiology and pathogenesis of cervical cancer, the state and sensitivity of Pap screening and the association between HPV infection and cervical cancer was sought for.

Information on the current stage of development of a prophylactic HPV vaccine, duration of conferred immunity, ideal age of vaccination and cost-effectiveness calculations were searched for. Regarding vaccine efficacy and safety randomised controlled double blind trials published between 2002 – 2005 were identified. First results from the Phase III clinical trials currently underway were also included.

Data on public knowledge about papilloma viruses and their association with cervical cancer and the societal acceptability specially by parents towards a vaccine against HPV was searched for.

Textbooks were refered for detailed literature on the background and developments over the past decades. Grey literature including newsletters like HPV Today and general newspaper articles served as an additional source of information.

The proceedings, abstract books and posters of recent international conferences in Europe on HPV and cancer related diseases were reviewed (including the EUROGIN 2004, the "HPV

and cancer" conference in Berlin/Germany 2005, the 2nd European conference on Cervical cancer screening in Tuebingen/Germany 2005 and the ECCO 2005 in Paris.) Experts and researchers in this field were contacted for information regarding the situation and HPV vaccination and cost/benefit analysis for Germany.

Contact was taken up to pharmaceutical companies involved in the research and development of candidate HPV vaccines for unpublished data.

The websites of the World Health Organisation and the Centres for Disease Control were studied. In addition websites of Institutions working on the national level (Germany) which included the Robert Koch Institut, the Bundeszentrale fuer Gesundheitliche Aufklaerung and Gesundheitsberichterstattung des Bundes were consulted for recent information on vaccination state in general and the current state of work on HPV vaccination. Data on cancer statistics regarding cervical cancer in Germany and Europe were obtained from the documentation of the population based national cancer registry.

5.   Results

Case-control studies, case series and prevalence surveys have all demonstrated that HPV DNA can be detected in 90% - 100% of properly collected and prepared cervical cancer specimens compared to 5% - 20% in the cervical cell samples of suitable epidemiological controls, given the use of modern detection methods like the HCII method.[16]

5.1   Type specific distribution of the human papillomavirus

A pooled analysis which used data from an international survey and from 10 multicentre case control studies co-ordinated by the IARC, determined the prevalence and geographical variation of HPV types found in cervical cancer. The analysis was based on 3,085 HPV pos. cervical cancer cases from 25 countries. Centralized HPV DNA detection methods were used. Of the 30 HPV types detected HPV type 16 was associated with 57.4% of cases and HPV 18 was seen in 16.6% of cases. Hence these two types were the most prevalent seen in 74% of all cases worldwide. The next 5 types (45, 31, 33, 52 and 58) accounted for 19.6% of cases.[57]
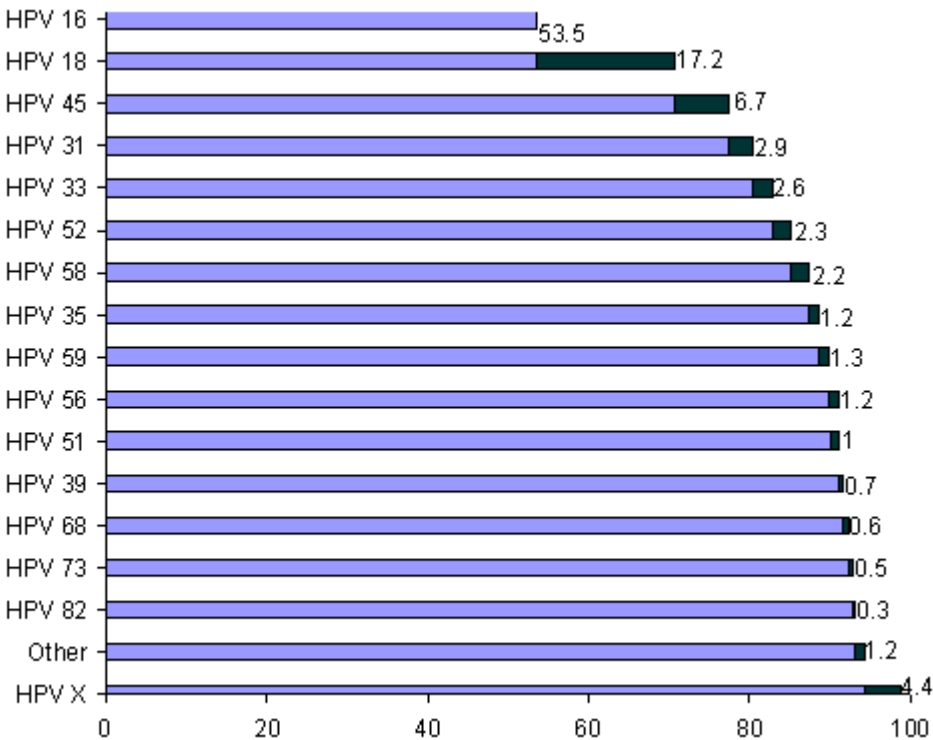

Figure 9: Cumulative percentages of cervical cancer cases attributed to HPV types in descending order in all world regions

Source: Taken from Munoz et al. Against which HPV types shall we vaccinate and screen[57]

5.2 Geographic Variation

Although HPV 16 and 18 were the most common types in all regions they showed considerable geographic variation, while 63.9% cases in sub-Saharan Africa were attributed to these two types, they accounted for 71.5% cases in Europe/North America, 73.5% cases in south Asia, 78.9% cases in northern Africa and 65% cases in central/south America. The prevalence of HPV 18 is comparatively high in south Asia, it was the predominant type identified in Indonesia.[58] HPV 45 was found to be more common in Sub-Saharan Africa (15%) while HPV 31 was the third most common type in Central/South America.

Current HPV vaccines confer type specific immunity hence these results have important implications in assessing the type specific burden of disease and the possible number of cases that could be prevented by a type specific prophylactic vaccine or a combination vaccine of different HPV types. An HPV 16 / 18 vaccine could ideally prevent 71.5% of cervical cancer cases in Europe / North America.
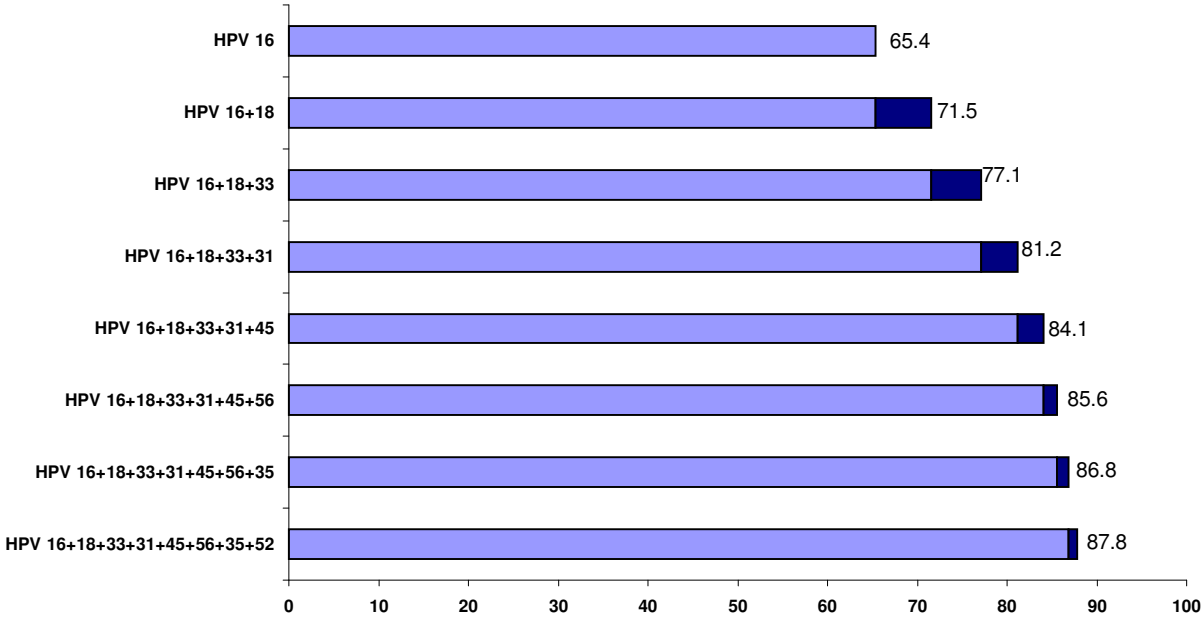

Figure 10: Cumulative percentages of cervical cancer attributed to the most frequent HPV genotypes in Europe and North America
Source: Taken from Munoz et al. Against which HPV types shall we vaccinate and screen [57]

Table 4:

Summary of randomized controlled clinical trials that assessed the vaccine efficacy of mono & polyvalent prophylactic L1 VLP HPV vaccines [59,60,61]

	Clinical Trial 1	Clinical Trial 2	Clinical Trial 3
Study			
Year	2002	2004	2005
Reference	Koutsky et al.	Harper et al.	Villa et al.
Design	RCT	RCT	RCT
Type of vaccine used	HPV-16 L1 VLP	HPV-16 & 18 L1 VLP	HPV types 6, 11, 16, 18 L1 VLP
No. of participants	1533	1113	552
received vaccine	768	566	277
received placebo	765	553	275
Age at vaccination	16 - 23 years	15 - 25 years	16 - 23 years
HPV status at enrollment	HPV-16 neg. till month 7	HPV neg. for 14 HR-HPV types	HPV neg. for types 6, 11, 16 & 18
Dose of vaccine	40 µg	20 µg HPV-16, 20 µg HPV-18	dose range: 20 - 80µg each
Vaccination schedule	0, 2 and 6 months	0, 1 and 6 months	0, 2 and 6 months
Duration of follow-up	median of 17.4 months	upto 27 months	36 months
Trial endpoints	persistent infection		persistent infection or disease
		18 months // 27 months	
Vaccine Efficacy			
in preventing incident/transient infection	91.2% (CI: 80 - 97)	91.6% (CI: 64.5 - 98.0) // 73.6% (CI: 49.7 - 86.1)	-
vaccine group	6 cases	2 cases // 12 cases	-
placebo group	27 cases	23 cases // 41 cases	-
in preventing persistent infection	100% (CI: 90 -100)	100% (CI: 47.0 - 100) // 100% (CI: 76.8 - 100)	90.0% (CI: 71 - 97)
vaccine group	No cases	No cases // No cases	4 events
placebo group	41 cases	7 cases // 16 cases	36 events
in preventing CIN/ cervical disease	100% (CI: 90 - 100)		100% (CI: 16 - 100)
vaccine group	No cases	No cases	No events
placebo group	9 cases	6 cases	6 events (CIN: 3 cases, External genital warts 3 cases)
Geometric mean titer of HPV	1510mMU/ml (at month 7)	HPV-16: 801.4 ELISA units/ml at 18 months HPV-18: 480.5 ELISA units/ml at 18months	HPV-6: 552Mmu/L (7 month), 93Mmu/L (36 month) HPV-11: 697Mmu/L (7 month), 94Mmu/L (36 month) HPV-16: 3892Mmu/L (7 month), 509Mmu/L (36 month) HPV-18: 801Mmu/L (7 month), 60Mmu/L (36 month)
Seroconversion	99.7%	100%	at 7 months 100% at 36 months: 94% for HPV-6, 11 & 16. 76% for HPV-18

5.3   Vaccine Efficacy

L1 VLP vaccines against 2 HR-HPV types (16 & 18) associated with 50 – 70% of cervical cancers and 2 LR-HPV types (6 & 11) responsible for over 90% of genital warts have been developed and tested. Three randomized placebo controlled phase II trials conducted to determine the vaccine efficacy, safety and immunogenicity of monovalent, bivalent and multivalent HPV L1 VLP vaccines have been summarized in the Table 4. All studies show the vaccines to be highly efficacious both in preventing persistent infection of the vaccinated HPV types the efficacy ranging between 90% - 100% and a 100% vaccine efficacy was demonstrated in preventing the development of precancerous cervical lesions.[59,60,61]

The clinical trial 1 evaluating the vaccine efficacy of the HPV type 16 vaccine (Table.2) has by now been followed up over a median period of 40 months post completion of vaccination and shows a 94% efficacy against persistent infection and a 100% efficacy against HPV-16 related CIN. 44 cases of CIN not associated with HPV-16 were seen among the 1533 participants, 22 out of 768 in the vaccine and 22 out of 765 in the placebo group. Evidence suggests that these HPV VLP vaccines provide only minimal or no cross-protection against other HR-HPV types.[59]

The vaccination ages in these trials ranged between 15 and 25 years. Preliminary results from a phase III trial where immune response between two age groups, one group aged 10 – 15 and the other aged 16 – 23 were compared revealed that geometric mean titres (GMT) of antibodies were 1.6 – 2 times higher in the 10 – 15 year age group.[62]

A close to 100% seroconversion was seen in the vaccine group of all studies. The geometric mean titers (GMT) of antibodies against the vaccinated HPV types were 60 – 100 times higher than those observed in naturally occurring HPV infection. In the clinical trial 1 the GMT observed in naturally occurring HPV-16 infection was 25.7 mMU/ml (milli merck units) versus an average GMT of 1510 mMU/ml in those receiving HPV-16 L1 VLP vaccine.[59]

An immunogenecity trial revealed that the HPV antibody titers were highest at month 7 (1 month post completion of vaccination regimen) declining rapidly in the initial months thereafter till a plateau is seen around 18 months. The GMT observed at 24 months were 3.9 – 9.3 fold higher to those seen in naturally occurring infections. This trial also evaluated the immune response in baseline HPV-16 seropositive subjects and found that the serum L1 antibody levels increased faster, peaked at higher levels and also remained at higher levels

after 24 months i.e. 2.4 to 3.5 fold higher then those subjects who were seronegative at baseline.[63] The minimum level of serum L1 HPV antibody levels associated with protection from HPV infection have not been defined as yet.[59,60,61,63]

The vaccines were found to be safe and well tolerated in all three trials as no significant adverse effects were seen in the vaccine group nor was there a notable difference in side effects between the placebo and vaccine groups.

Phase III clinical trials with more than 25,000 participants worldwide are currently underway. Preliminary results of the FUTURE II trial with 12,167 women aged (16 – 23) followed over 2 years have shown the vaccine to be 100% effective in preventing HPV-16/18 associated CIN2/3 in the population group without protocol violations and 97% effective in the group with protocol violations.[64,54]

5.4   Modelling Studies

A comprehensive natural history model of HPV infection and cervical cancer estimated the impact a prophylactic HPV 16/18 vaccine using a computer based mathematical model. It incorporated the type specific HPV distribution in precancerous lesions and invasive cancer and also explored the impact using alternative assumptions on vaccine efficacy, coverage, wanning immunity and competing risks associated with non HPV 16/18 oncogenic types in vaccinated women.

A vaccine that would prevent 98% of persistent HPV 16/18 infections would lead to a similar reduction in the HPV16/18 associated cancers and a 51% reduction in the overall incidence of cervical cancers. A vaccine efficacy of 75% would result in a 70 – 83% reduction of HPV 16/18 cancers and a 44% reduction of all cervical cancers. These figures are based on the assumption that the cumulative number of cancers caused due to non 16/18 HPV types would increase as can be seen in Fig.11 due to the competing risk associated with the other oncogenic types.[65]
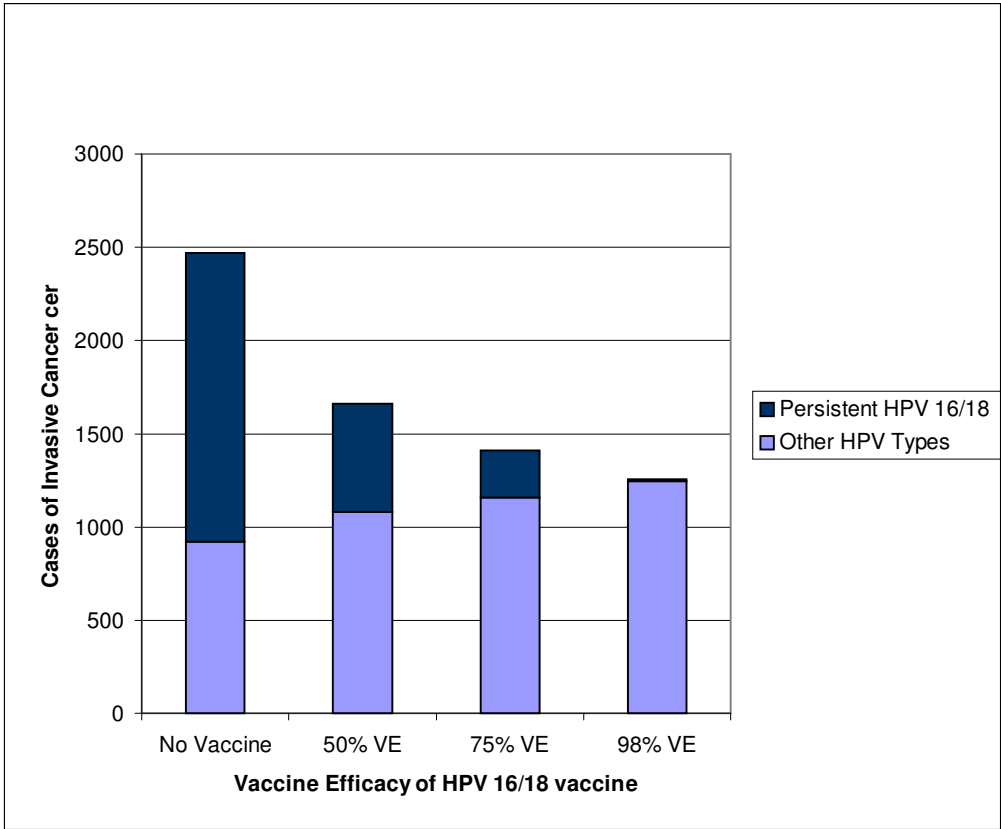

Figure 11: Effect of vaccine efficacy of a HPV 16/18 vaccine and competing risk of non 16/18 HPV types on the incidence of invasive cervical cancer.
Source: Taken from Goldie et al. clinical impact of a prophylactic HPV-16/18 vaccine [65]

The proportion of the at risk population successfully vaccinated has a profound impact on the benefits of a HPV16/18 vaccine and hence reduction of cervical cancer incidence, also independent of vaccine efficacy. As seen in Fig.12 a broad vaccine coverage of at least 75% of the at risk population with a partially effective vaccine (50 – 75% VE) is more effective than a vaccine coverage of 50% or less with a highly effective vaccine.[65]
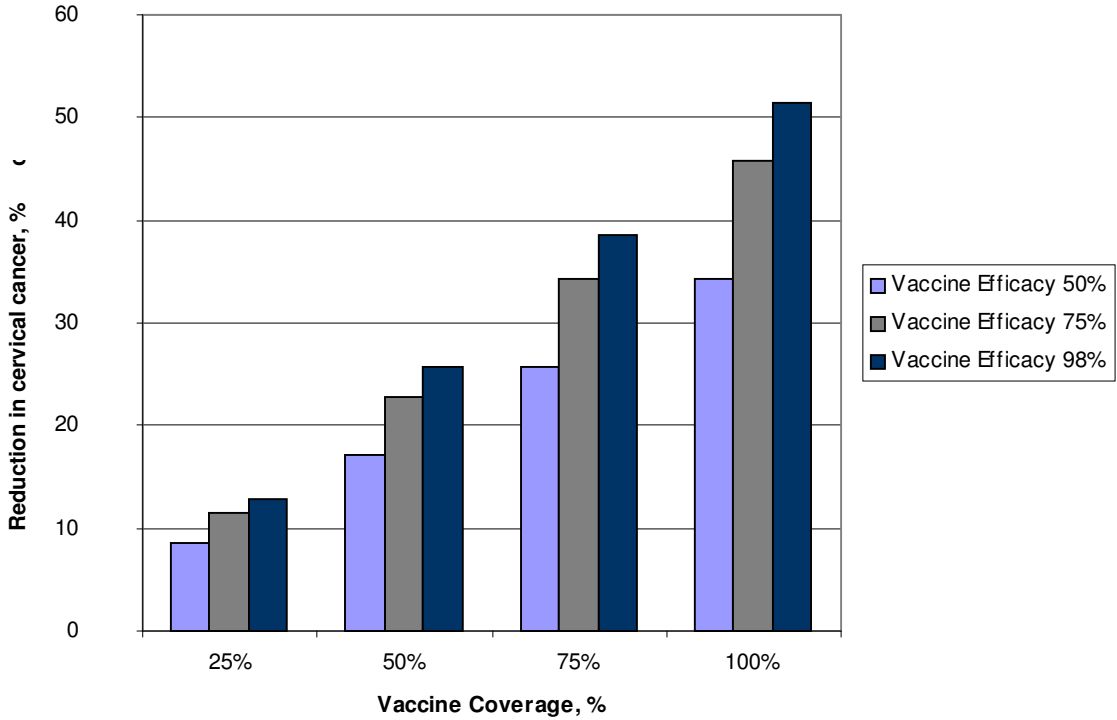

Figure 12: Impact of HPV-16/18 vaccine coverage rates on reduction of invasive cervical cancer considering different vaccine efficacies
Source: Taken from Goldie et al. clinical impact of a prophylactic HPV-16/18 vaccine [65]

There is no exact definition of viral persistence and it in not clear which HPV infection actually leads to invasive cancer, those acquired shortly after initiation of sexual activity or those acquired later in life. The proportion of cervical cancers caused by previously acquired or latent infection versus those attributable to infections acquired at a later stage play an important role in determining the effect of wanning immunity of a HPV 16/18 vaccine on prevention. On assuming a vaccine efficacy of 75% as shown in Fig.13 the model calculated the effect that a 25, 50, 75 or 100% reduction in the protective immunity conferred by the vaccine after a period of 10 years would have on the incidence of cervical cancer, if 100% of cases, 50% of cases or none of the cervical cancer cases were attributable to either latent infections or to newly acquired infections.[65]

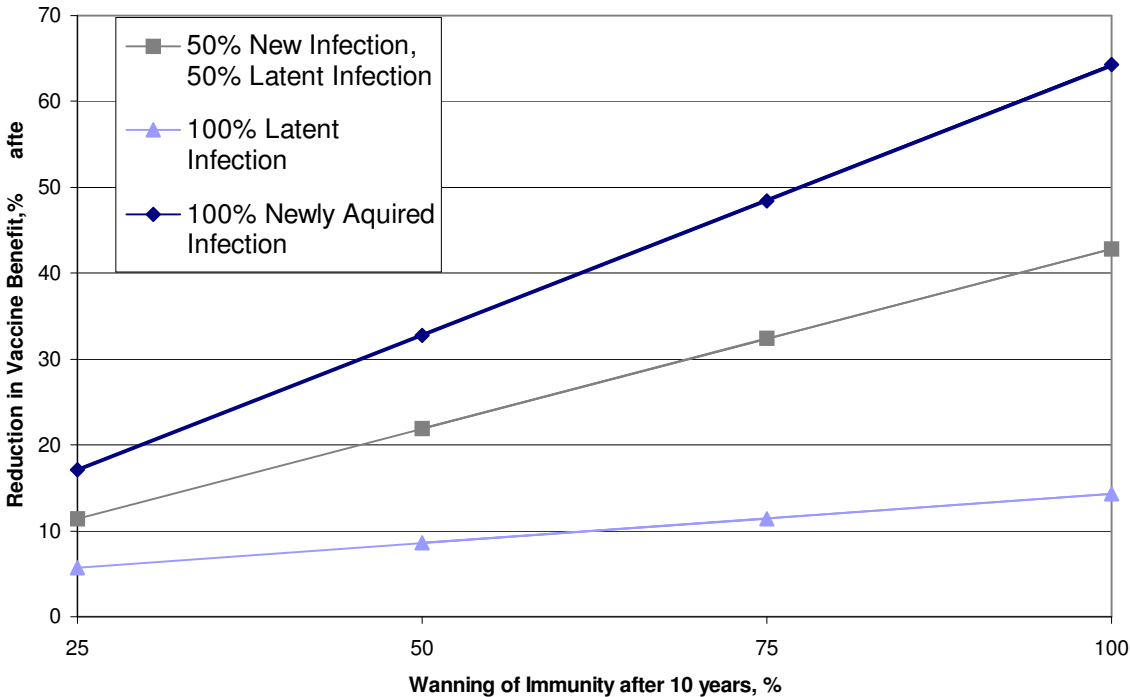**Figure 13: Impact of wanning immunity on incidence of invasive cervical cancer after 10 years considering**
         1: 100% cases attributable to previously acquired latent infection
         2: 50% cases attributable to latent & 50% to newly acquired infection
         3: 100% cases attributable to newly acquired infection
Source: Adapted from Goldie et al. clinical impact of a prophylactic HPV-16/18 vaccine [65]

This model was calibrated to data from Costa Rica, in Europe and North America where according to the data from the pooled analysis HPV-16/18 are associated with 71.5% of cervical cancers the proportion of cervical cancer cases prevented maybe higher.[65]

A study investigating the theoretical population-level impact of a HPV vaccine using a transmission model assuming, a 90% vaccine coverage, a 75% vaccine efficacy and a mean duration of immunity for 10 years came to the conclusion that vaccinating both men and women against a specific type of HPV would result in a 44% decrease in prevalence of that particular type while vaccinating only women would lead to a 30% reduction in prevalence. The female only strategy is 60% - 75% as efficient as a strategy targeting both sexes.[74]

The actual reduction in the incidence of carcinoma in situ (CIS) and invasive cervical cancer is smaller then the reduction in HR-HPV infections, for e.g. a 60% reduction in overall HPV infection would result in 46% reduction of CIS and 47% reduction in invasive cervical cancer. This is considered to be due to the replacement of the HPV types avoided by vaccination by other HR-HPV types.[74]

5.5   Cost-effectiveness Analysis

The aim of a cost effectiveness analysis is not to determine which measure is associated with the minimum costs rather it provides a tool for evaluating the efficiency of resource utilization i.e. how much health improvement can be gained for each extra unit of expenditure. The results are expressed as incremental cost-effectiveness ratio which compares the health outcomes divided by associated costs of one strategy with the next most effective alternate strategy.[66] Cost-effectiveness ratios of less than $75,000 per quality adjusted life year (QALY) gained are considered as good value for resource for a country like the USA.[67]

A decision analytic model designed to explore the clinical benefits and cost-effectiveness of introducing an HPV 16/18 vaccine in a population where organized cervical cancer screening programs exist, compared cytologic screening with a combined strategy of vaccination and screening.

When calculating the cost-effectiveness of introducing an HPV16/18 vaccine in the present cervical cancer screening practice in the US, such a vaccine with an efficacy ranging from 70% - 100% would reduce the lifetime risk of cervical cancer by 46 – 66% compared with

current screening assuming that the screening practice does not change. The incremental cost-effectiveness ratio of an HPV16/18 vaccine with a 90% efficacy would be $24,300/QALY.[68]

The model then compared different vaccination (different ages) and screening (conventional or liquid based cytology) strategies and showed that the most effective strategy with an incremental cost-effectiveness ratio of less than $60,000 per quality adjusted life year would be a combination of vaccination at the age of 12 years together with conventional cytologic screening every three years starting at the age of 25 years. This would reduce the life time cervical cancer risk by 94% compared to no intervention. Increasing screening frequency would have a small influence on the reduction of life time risk yet cause a substantial increase in costs. The study concluded that a vaccine that prevents atleast 70% of persistent HPV16/18 infections could substantially reduce HPV16/18 associated cancer even in a setting where cytologic screening is established.[68]

The benefits and cost effectiveness of introducing an HPV16/18 vaccine for girls or for both sexes, considering the effect of herd immunity, the long-term sequel of HPV infection for men which is generally less serious and that men act as vectors for infection were evaluated. The model included different risk and age groups, it assumed, an HPV-16/18 vaccine with an efficacy of 90%, a vaccine coverage of 70% targeting only girls and protective effect of the vaccine lasting for 10 years. Vaccine cost of $300 for the initial vaccination (three doses) and $100 for the booster were assumed. The study concluded that an HPV-16/18 vaccine for 12-year-old girls would reduce cohort cancer cases by 61.8% compared to prevaccination level, with a cost-effectiveness ratio of $14,583 per quality-adjusted life year (QALY). Including male participants in a vaccine programm would further reduce cervical cancer cases by only 2.2% at an incremental cost-effectiveness ratio of $442,039/QALY compared with female-only vaccination and would hence not be cost-effective.[69]

5.5.1   Situation in Germany

Similar cost-effectiveness analysis taking into account the German screening practice and costs associated with screening and cervical disease have not been conducted as yet. According to the German national health survey 22,977 patients with the diagnosis of cervical cancer were hospitalized in the year 1995. This accounts for 0.2% of all hospitalizations during that year. The average duration of hospital stay for these patients was 13 days.[70]

Data from an unpublished study presented at the ECCO 13 conference in Paris estimates the annual costs associated with the management of cervical dysplasias (Pap III, IIID and IV) in Germany in the year 04/05. Direct costs included specialists visits, diagnostic tests and intervention while the indirect non-medical costs included productivity loss.

The study included 138 randomly selected patients who were treated over a median period of 4.5 months, 99% of them received a Pap smear cytology, followed by a colposcopy in 75% or curettage in 25% of cases. 29% were treated by conization, 9% had a hysterectomy, 5% received laser coagulation therapy and 53% required no intervention. 1/3 of the patients were hospitalized for a median duration of 5 days and about 50% of patients took sick leave for a median of 12 days. The total average costs per patient were estimated at €1,521 (95% CI: €1,163 - €1,914). Approximately 40% of the costs are indirect costs. The main cost contributors are interventions and productivity loss. A vaccine preventing most cervical lesions could potentially avert much of these costs from the German healthcare system.[71]

In addition a vaccine targeting the low risk HPV types 6 and 11 is most likely to substantially reduce the incidence of condyolmas and genital warts 90% of which are associated with these two types. This would lead to a decrease in health care expenditure and make the vaccine even more cost-effective(69). It would also reduce psychological stress and morbidity associated with this condition which afflicts about 1% of the population.[54]

5.6   Impact of Vaccination

As the best age to vaccinate is shortly before initiation of sexual activity, a vaccination of girls around the age of 12 is unlikely to achieve a vaccine coverage of 90% or more as seen for the common childhood vaccinations. The level of vaccine coverage specially in the western German states reduces with age, as booster vaccination recommendations are not followed.
Yet the acceptance of vaccination has been improving as seen by the increasing rates of vaccination in the child and adolescent health survey of 1996 and 2002.[72] Vaccination rates against Hepatitis B which is a recommended childhood vaccination since 1995 have increased from 68% in 2002 to 84% in 2004.[73]

Assuming the HPV type 16 and 18 distribution of Germany to be similar to that for Northern Europe i.e. 71.5%, probably the majority of the 6580 incident cases of invasive cervical cancer and the 30 –100 fold higher number of precancerous lesions are caused by these two

HPV types. A vaccine efficacy of around 90% seems to be realistic as has been proven in several randomized control trials. Vaccinating girls with a highly effective multivalent HPV L1 VLP vaccine having an efficacy of 90% given a high vaccine coverage would lead to a substantial reduction in both the of number of precancerous lesions and cervical cancer cases. Making a quantitative statement as to the exact number of cases prevented would be too vague as long term data on duration and efficacy of the vaccine is not available and more data from large scale studies on disease transmission dynamics and acceptance of the vaccine in Germany would be needed. Based on the current level of knowledge a vaccine with this safety profile and efficacy should significantly decrease the burden of disease caused by cervical cancer in Germany in a cost-effective manner.

6.   Discussion

From a scientific and technical perspective, vaccination with HPV L1 VLPs has delivered promising results. Prevention of infection by HR-HPV types by vaccination may prove to be the most efficient and logistically feasible intervention.[16] Phase II trials of both mono and polyvalent HPV vaccines have shown a 100% efficacy in preventing CIN over a follow up period of upto 48 months as have the preliminary results of the phase III trials. In addition a variety of calculation models have indicated a HPV vaccination programm to be cost effective. This makes the prospect of preventing more than 50% of invasive cervical cancers and a much higher number of precancerous cervical lesions, an attractive possibility. For the successful and effective implementation of HPV vaccination in public health programs on a large scale several practical issues must be addressed.[32,28]

6.1   Vaccine coverage in Germany

An extensive child and adolescent health survey (2001 –2002) revealed that the percentage of protective immunization is highest in the 2 – 6 years old age group with vaccine coverage ranging from 86 –96% for the recommended childhood vaccinations. In the 7 – 11 year age group the vaccine coverage for Diphtheria and Tetanus is still high yet for the MMR vaccine it reduces to 75%(east) and 59%(west). This reduction reflects the reluctance of obtaining the second (booster) MMR vaccine which has now been recommended to take place before the age for 2 yrs. with the hope of achieving a better coverage. The level of immunization noted in the 12 – 17 year old age group is highly unsatisfactory, being partly due to the lack of booster vaccination acquired in that age group. There is an enormous disparity between the former east and west German states, while the levels of vaccine coverage for diseases like Diphtheria and Tetanus is around 47% in the western part it is close to 95% in the eastern German cities.[47]

The child and adolescent health survey checking for the vaccine coverage of children at school entrance revealed that when comparing the vaccine coverage rates of 1996 with those of 2002, a general increase in vaccine coverage can be observed for all childhood vaccines. This trend is specially noticeable for the Pertussis, Hepatitis B and MMR vaccines.[72] This maybe a reflection of an increasing vaccine acceptance among parents in general.

Vaccination has been one of the most effective means for prevention against a large number of infectious diseases, thereby not only reducing morbidity and mortality but also saving enormous costs both for individuals and for society. This reduction in vaccine coverage seen

with age will make it particularly difficult to achieve high vaccination levels for HPV vaccines.

6.2   Trends in sexual behaviour of adolescents

The pattern of sexual activity, especially in teenagers, is a major factor in determining whether a person becomes infected with HPV. As a result of relaxed attitudes about sexuality among adolescents in many cultures, the number of sexual partners that teenagers have before age 20 has increased, and each partner may also have had multiple partners.[52]

A representative survey conducted in 2001 in Germany showed that about 35% of girls and 31% of boys have their first sexual experience between the age of 14 -17 years. Among the 14 year old age group nearly 10% have been sexually active. Compared to 1980 the number of sexually active adolescents has greatly increased.[53] Consequently this pattern of sexual activity is the reason for the increasing incidence of HPV infection and CIN.[54]

6.3   The pros and cons of different vaccination ages for HPV

A prophylactic HPV vaccination programm will be most beneficial if it targets adolescent girls before commencement of sexual activity. Implementing such a vaccination programm will be difficult as there are no routine measures that bring pre-adolescent girls to a clinic three times over six months. In Germany since 1998 all adolescents aged 12 – 14 years are entitled to the J1 (Jugendgesundheitsuntersuchung) a comprehensive medical check-up which also includes catch-up and booster vaccination. Its utilization is highly unsatisfactory though with only 5 – 25% of adolescents availing this service.[55] Introducing HPV vaccination in the school setting could be a feasible option as was seen for Rubella vaccination of school girls in the 80's.

Due to the earlier initiation of sexual activity, many teenagers visit office based gynaecologists at an earlier age for prescription of oral contraceptives, at this stage a catch-up vaccination could be recommended for all those who have not received the vaccine.

Experience with vaccines has shown that the highest vaccine coverage is achieved when vaccinating infants hence vaccine coverage would probably be improved if the vaccine is taken up into the infant immunization programm followed by a booster vaccine at the age of 12 years. In Germany the incidence of Hepatitis B rises after the age of 15 years and is

predominantly transmitted sexually (36%) and by intravenous drug abuse (7%) yet it is part of the infant immunization schedule.[73]

In addition vaccinating at an early age generally leads to a more potent immune response, and when followed by a booster vaccine confers a longer lasting immunity. As the duration of protective immunity is not known and no studies have been conducted in age groups younger than 9yrs. it is not an option at this stage but might become so in future.

Focusing on 12-year-olds would be more cost-effective than focusing on infants. If a vaccination program focusing on infants were more widely accepted, with initial coverage of 80%, only a slight increase in the lifetime cervical cancer cases prevented is expected i.e. 63% instead of 61.8%, and the cost-effectiveness ratio would reduce to $28,181/QALY.[69]

A catch-up vaccination for 24 – 30 year old women may reduce the lifetime cancer risk by 17 – 35% according to model calculations even in this age group.[69] Vaccinating women who are sexually active would protect those who have not been infected with the HPV genotypes contained in the vaccine. For those women who are infected with the vaccine HPV types it could protect against the development of cervical cancer by decreasing the persistence of infection and it might also decrease the likelihood of transmission to sexual partners.[50] It would most likely also enhance the acceptance of parents to vaccinate their children.

The first cohort of vaccinated adolescents will experience a smaller reduction in cancer cases because many of their sex partners will be drawn from a population pool that has not been vaccinated.[69]

6.4   Factors Influencing Vaccine Coverage

6.4.1   Reasons for non compliance

In Germany the vaccination of infants, children and adults is voluntary and hence knowledge and acceptance of vaccination plays a major role for successful implementation of a vaccine programm. It is estimated that about 2% of the population are absolutely opposed to all kinds of vaccination while about 10% of parents have reservations against some of the vaccines recommended by the STIKO (Staendige Impfkomission). The major reason for failing to achieve high degrees of immunization is the lack of knowledge about the transmission and

consequences of the disease. Ignorance about the availability and effectiveness of vaccines and fear of adverse effects associated with vaccination as well as negligence.[72]

6.4.2   Knowledge about HPV

A population based survey carried out in a German city to assess the utilization of cancer screening programs and the knowledge of risk factors for cervical cancer revealed that only 3.2% of the participants knew that human papillomavirus infection is a risk factor for cervical cancer. The study also revealed that the main source of information for the women, regarding risk factors were the office based gynaecologists (69.2%) followed by the media (53.8%) which included both print media and television.[46]

Physicians have an enormous influence on people both by spreading information and also by giving their recommendation. This effects the motivation and acceptance of people/parents towards vaccination. A large number of studies have shown that approx. 85% of people follow the recommendation of their physician.[72]

The importance of continuos professional education specially of health professionals related to this field is evident. Paediatricians commonly deal with vaccination against infectious diseases, yet cervical carcinoma and genital warts are diseases they rarely encounter. Detailed information on HPV and the pros and cons of vaccination and the latest developments are necessary. The physicians may have become tired of motivating parents to vaccinate their children which might be still more difficult with a vaccine against a sexually transmitted disease. Appropriate ways on how to inform parents and children about the possibility of prevention need to be adopted.

A comprehensive public health education programm utilizing print and electronic media in a way which is sensitive to the concerns of the parents will be important to create awareness. In addition the school setting could be used to inform adolescents in an adequate way on the risk factors and modes of prevention.

6.4.3 Vaccine acceptance

An additional difficulty encountered with HPV vaccination is the stigma that is associated with a sexually transmitted infection. Parents maybe reluctant to vaccinate their daughters against a sexually transmitted infection at a young age.[50,28,32]. Studies conducted in the US to assess the attitude of women towards vaccinating their children showed that around 70% of women would consent to get their daughters vaccinated. Reasons for objection included fear of side effects and that minors are not sexually active.[48] Parents might think this matter could be addressed later in life. An important concern among parents is that they fear vaccinating their children against a sexually transmitted disease might promote children to become sexually active at an earlier age. An educational intervention proved effective in alleviating some of the concerns and improving acceptability.[49]

To improve the acceptance of this vaccine it has been suggested to maintain a philosophical distance to the sexual aspects and instead focus on the prevention of cancer.[28,32] It would be deceptive to ignore the sexually transmitted nature of the infection, an option would be to explain its similarities to hepatitis B infection, which in developed countries is spread to a large extent in a similar manner.

6.4.3 Socio-economic barriers

In countries with organized cervical cancer screening programs approx. 50% of cervical cancers are seen in women who do not attend screening regularly.[50] The higher incidence of cervical neoplasia and the lower utilization of screening programs in the lower socio-economic class is also evident in Germany.[51,45] This implies that these population groups should be specially targeted while designing mass education programs and vaccination strategies. If the vaccine compliance in this vulnerable group is lower it would reduce the population benefits considerably.

6.5 Properties of an ideal vaccine

An ideal prophylactic vaccine needs to possess several attributes. It should be safe, because it would be given to young, normal individuals, the vast majority of whom, even without a vaccine, would not be expected to develop cancer from HPV infection. It should be inexpensive, and effective after a single dosage, be useable in combination with other

vaccines and be easy to handle. Protection should last for many years and the vaccine should confer a substantial reduction in the incidence of cervical cancer. The VLP vaccine fulfils these criterias to some extent, as an empty capsid vaccine devoid of DNA it has proved to be safe in all trials. A combination vaccine of HPV and Hepatitis B has been used in phase III trials in Germany. Unfortunately the HPV vaccine does not cover all oncogenic HPV types and cross protection against non vaccine types is unlikely hence a close to 100% protection against cervical cancer in those vaccinated is not possible.

6.5.1   Duration of protection

Follow-up studies of vaccine efficacy do not exceed 48 months, the decline in serum L1 antibody levels observed in all studies, requires long term follow up of the trial participants to determine the minimum serum antibody levels required to prevent infection and the duration of protection conferred by the different HPV type vaccines.[63] In addition it is essential to monitor the effect of vaccination on non vaccine HR-HPV types and the incidence of CIN. The Finnish cancer registry has enrolled 25,000 (Vaccinated/Unvaccinated) young women aged 16 – 19 years to assess the long term effects of the intervention upto 2015.[56]

6.5.2   Vaccine costs

The cost of this vaccine which has been estimated around US $80 – $100 per dose is very high considering that other childhood vaccines cost about 1/3 of the price in Europe.
This makes the vaccine extremely expensive for developing countries where immunization against HPV may bring the greatest benefit as >80% of cervical cancers are found there and less than 5% of women undergo cervical screening.[50] In addition these vaccines require a cold chain making proper handling more difficult and expensive.

6.6   Impact of vaccination on cervical cancer screening

In countries with effective population-wide cervical cancer screening programs the incidence of invasive cervical cancer reduced by more than 80% since their implementation.[50] Considerations are whether the introduction of a vaccine might be able to reduce the physical, psychological, and financial costs associated with screening and follow-up through a reduction in the frequency of detection of cervical abnormalities and possibly the frequency of

screening.[28] Atleast 25 – 30% of cancers are caused by types not included in the vaccines under trial, hence vaccination cannot replace screening.[50]

Cost-effectiveness analysis comparing different screening frequencies in the present US situation show an immense increase in costs of more than $500,000 per year of life saved (YLS) when increasing the screening frequency from every two years to every year. The cost-effectiveness ratio improves to $60,000/YLS for triennial screening.[66]

Considering these calculations, the protective immunity conferred by the vaccine and the slow development of cervical lesions owing to the long latency period, increasing the intervals between Pap screening could be an option in future.

Even after introduction of vaccination it will take some years before a reduction of cases is detectable at population level and hence existing screening programs should continue until results from long term studies are available.[25]

A reduction in the compliance with Pap screening programs due to false assumptions by women, to be protected against all cervical cancers after vaccination could greatly minimize the benefits conferred by vaccination or even lead to an opposite effect.[50]

6.7   Endpoint for vaccine efficacy

Traditionally, in etiological and cancer prevention studies, the measurable end point to determine efficacy of an intervention has been the incidence of cancer itself. In the case of cervical cancer, a disease that can be prevented through proper detection and treatment, a study end point of cancer is both ethically impracticable and lengthy. The WHO consultation recommended the endpoint for vaccine efficacy in population based studies to be both histologically confirmed moderate or high grade CIN and cancer. Cytological testing (Pap test) due to its lower sensitivity (false negatives) would be inaccurate. The U.S. Food and Drug Administration endorsed the recommendation making it the primary end point for vaccine licensure in the U.S.[25]

6.8   State of Vaccine licensure

The pharmaceutical companies Glaxo and Merck are involved in the development of polyvalent HPV vaccines. Merck in Dec. 2005 applied for licensure of the tetravalent vaccine

Gardasil (HPV-6, 11,16 &18) with the FDA and also with European and Australian licensing authorities. For Germany the Paul-Ehrlich Institute is incharge for licensure and approval of new vaccines before they are evaluated by the STIKO (Staendige Impfkommision) which is the authority responsible for vaccine recommendations in Germany. Uptill now this process has not been initiated for the HPV vaccine in Germany (telephonic communication)

6.9   Conclusion

Decision making in public health is a process that uses scientific evidence in addition to judgement and socio-economic considerations. The turning point at which public health decisions are taken as opposed to waiting for additional research results is often difficult to find.

If prophylactic vaccination were instituted on a worldwide scale today, it would take decades (because of the long latency from HPV infection to the development of cervical cancer) to perceive the benefits; that is, lower incidences of cervical preinvasive and invasive disease.
Many important questions regarding the actual quantitative reduction of cervical disease cases, the duration of protective immunity, if and at what interval booster vaccination would be required, whether an acceptable vaccine coverage is achieved, whether screening intervals can be extended and whether vaccination is finally able to reduce health care costs remain to be answered. Most of the data on disease transmission, cost-effectiveness and acceptance of the vaccine have been obtained in the US, studies refering to the German situation are needed.

These questions concerning the actual effectiveness can only be answered by implementing vaccination programs on a large scale in the real life situation. Yet waiting for decades until all questions are answered would be unethical considering the benefit it may bring to a large number of women.

7.   References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global Cancer Statitics, 2002. CA Cancer J Clin 2005;55:74-108
2. Krebs in Deutschland: Haeufigkeiten und Trends. Arbeitsgemeinschaft Bevoelkerungsbezogener Krebsregister in Deutschland, Robert Koch Institut. 4. ueberarbeitete Ausgabe, Saarbruecken, 2004
3. Boesartige Neubildungen: 5.7 Zervixkarzinom. GBE:Gesundheitsbericht fuer Deutschland. www.gbe-bund.de/pls/gbe
4. Bosch FX, de Sanjose S. Human papillomavirus and cervical cancer – burden and assessment of causality. J Natl Cancer Inst Monogr 2003:3-13
5. Syrjänen K, Hakama M, Saarikoski S, et al. Prevalence, incidence, and estimated life-time risk of cervical human papillomavirus infections in a nonselected Finnish female population. *Sexually Transmitted Diseases 1990;* 17(1):15– 19
6. Winer RL, Lee SK, Hughes JP et al. Genital human papillomavirus infection: incidence and risk factors in an cohort of female university students. Am J Epidemiol 2003;157:218-26
7. Franco, E. L./ Harper, D. M.: Vaccination against human papillomavirus infection: a new paradigm in cervical cancer control. Vaccine 2005;23: 2388-2394
8. Franco EL, Villa LL, Sobrinho JP et al. Epidemiology of acquisition and clearance of cevical human papillomavirus infection in women from a high risk area for cervical cancer. J Infect Dis 1999;180:1415-23
9. Ho GY, Bierman R, Beardsley L et al. Natural history of cervicovaginal papillomavirus infection in young women. N Engl J Med 1998;338:423-28
10. zur Hausen H. Viruses in human cancers. Science 1991; 254: 1167 – 1173
11. Rozendaal L, Walboomers JM, van der Linden JC et al. PCR based high-risk HPV test in cervical cancer screening gives objective risk assessment of women with cytomorphologically normal cervical smears. Int J Cancer 1996;68:766-9
12. Schneider A, Duerst M, Kaufmann AM et al. HPV-Infektion und Zervixkarzinom – Epidemiologie, Nachweis und Immunologie. Zentralbl Gynakol 2001;123:179-185
13. Koutsky LA, Holmes KK, Critchlow CW et al. A cohort study of the risk of cervical intraepithelial neoplasia grade 2 or 3 in relation to papillomavirus infection. N Engl J Med 1992;327:1272-1278
14. Walboomers JM, Jacobs MV, Manos MM et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol;189:12-19
15. Hollingworth RE, Lee WH. Tumor supperession genes: new prospects for cancer research. J Natl Cancer Inst 1991;83: 91-6
16. Bosch FX, Loricz A, Munoz N et al. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol 2002;55:244-65
17.   Cullen AP, Reid R, Campion M, Lorincz AT. Analysis of the physical state of different human papillomavirus DNAs in intraepithelial and invasive cervical neoplasm. J Virol 1991;65:606-12
18. Halbert CL, Demers GW, Galloway DA. The E6 and E7 genes of human papillomavirus type 6 have weak immortalizing activity in human epithelial cells. J Virol 1992;66(4):2125-34
19. Munoz N, Bosch X, Sanjose S et al. Epidemiologic classificaion of human papillomavirus types associated with cervical cancer. N Engl J Med 2003;348:518-27
20. Bosch FX, Rohan T, Schneider A, et al. Papillomavirus research update: highlights of the Barcelona HPV 2000 international papillomavirus conference. J Clin Pathol 2001;54:163–75

21. Schneider A, Duerst M, Jochmus I, Gissmann L. Epidemiologie, Aetiologie und Praevention des Zervixkarzinoms. Gynaekologe 1999;32:247-60
22. Boecker, Denk, Heitz. Pathologie. Verlag: Urban und Schwarzenberg (1997)
23. Burghardt E, Holzer E. Localization of the pathologic cervical epithelium. 1. Carcinoma in situ, dysplasias and abnormal squamous epithelium. Arch Gynakol 1970;209:305-330
24. Nanda K, McCrory DC, Myers ER et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytological abnormalities: a systematic review. Ann Intern Med 2000;132:810-19
25. Pagliusi SR, Aguado MT. Efficacy and other milestones for human papillomavirus vaccine introduction. Vaccine 2004;24:569-578
26. Bosch FX, Manos MM, Munoz N etal. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International Biological Study on Cervical Cancer (IBSCC) study group. J Natl Cancer Inst 1995;87: 770-80
27. Lawson HW, Lee NC, Thames SF et al. Cervical cancer screening among low-income women: results of a national screening program, 1991-1995. Obstet Gyneco 1998;l92:745-52
28. Mahdavi A, Monk BJ. Vaccines Against Human Papillomavirus and Cervical Cancer: Promises and Challenges. The Oncologist 2005;10: 528-538
29. Koutsky LA, Galloway DA, Holmes KK. Epidemiology of genital human papillomavirus infection. Epidemiol Rev 1988;10:122-63
30. www.hpa.org.uk/infections/topics_az/hiv_and_sti/sti-warts/epidemiology/epidemiology.htm. Health Protection Agnecy Guidelines. (23.11.05)
31. Eng TR, Butler WT. The neglected health and economic impact of STD's. The hidden epidemic: confronting sexually transmitted dieases, Committee on Prevention and Control of Sexually Trasmitted Disease, Institute of Medicine, National Academic Press,1997, pp 28-68
32. Jansen KU, Shaw AR. Human papillomavirus vaccines and prevention of cervical cancer. Annu Rev Med 2004;55:319–331
33. Ylitalo N et al. Smoking and oral contraceptives as a risk factor for cervical intraepithelial neoplasia. Int J Cancer 1999; 81(3): 357–365
34. Petry KU, Scheffel D, Bode U et al. Cellular immunodeficiency enhances the progression of human papillomavirus-associated cervical lesions. Int J Cancer 1994; 57(6):836-40
35. Laimins LA. The biology of human papillomaviruses: from warts to cancer. Infect Agents Dis 1993;2(2):74-86
36. Carter JJ, Galloway DA. Humoral immune response to human papillomavirus infection. Clin Dermatol 1997;15(2):249-59
37. Thomas KK, Hughes JP, Kuypers JM et al. Concurrent and sequential acquisition of different genital human papillomavirus types. J Infect Dis 2000;182:1097-102
38. Roden RB, Lowy DR, Schiller JT. Papillomavirus is resistant to desiccation. J Infect Dis 1997 ;176(4):1076–1079
39. Wen LM et al. 1999. Risk factors for the acquisition of genital warts: Are condoms protective? Sex Transm Infect 1999; 75:312–316
40. CastellsagueX, Bosch FX, Munoz N et al. Male circumcision,penile human papillomavirus infection, and cervical cancer in female partners. N Engl J Med 2002; 346:1105–12
41. Zhou J, Sun XY, Stenzel DJ et al. Expression of vaccinia recombinant HPV 16 L1 and L2 ORF proteins in epithelial cells is sufficient for assembly of HPV virion-like particles. Virology 1991;185:251–257

42. Nardelli-Haefliger D, Wirthner D, Schiller JT et al. Specific antibody levels at the cervix during the menstrual cycle of women vaccinated with human papillomavirus 16 virus-like particles. J Natl Cancer Inst 2003;95:1128–11

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

44. Prendiville W, Davies P. Human papillomavirus and cervical cancer. The Health Professional's HPV Handbook. The European Consortium for Cervical Cancer Education (ECCCE). Publised by: Taylor & Francis (www.tandf.co.uk)

45. Kahl H, Hoelling H, Kamtsiuris P. Inanspruchnahme von Frueherkennungsuntersuchungen und Maßnahmen zur Gesundheitsförderung. Gesundheitswesen 1999; 61(2):163-168

46. Klug SJ, Hetzer M, Blettner M. Screening for breast and cervical cancer in a large German city: participation, motivation and knowledge of risk factors. European Journal of Public Health 2005;15(1):70-77

47. Dippelhofer A, Meyer C, Kamtsiuris P et al. Robert Koch-Institut,Berlin. Erste Ergebnisse zum Impfstatus aus der Pilotphase des Kinder- und Jugendgesundheitssurveys. Bundesgesundheitsbl -Gesundheitsforsch – Gesundheitsschutz 2002; 45:332–337 © Springer-Verlag 2002

48. Slomovitz BM, Sun CC, Frumovitz M et al. Are women ready for the cervical cancer vaccine? Gynecol Oncol 2005;96:912

49. Davis K, Dickma E, Ferris D. Human Papillomavirus Vaccine Acceptability Among Parents of 10- to 15-Year-Old Adolescents. Journal of Lower Genital Tract Disease. 2004;8(3):188-194

50. Schiller JT, Davies P. Delivering on the promise: HPV vaccines and cervical cancer. Nature Reviews 2004;2(4):343-347

51. Richter M, Band H, Roessler G. Socio-economic differences in the utilisation of screening programms and health promotion measures in North Rhine –Westphalia, Germany. Gesundheitswesen 2002;64:417-423

52. Noel McIntosh, MD. Human Papillomavirus And Cervical Cancer. Paper No.8 May 2000 . JHPIEGO Corporation

53. Jugendsexualitaet: Wiederholungsbefragung von 14 bis 17-Jaehrigen und Ihren Eltern. Ergebnisse der Repraesentativbefragung aus 2001. Bundeszentrale fuer Gesundheitliche Aufklaerung

54. Lowndes CM, O Noel G. Cervical cancer, human papillomavirus, and vaccination. BMJ 2005;331:915-916

55. Philips EB, Bunzendahl I. Gesundheitsziele in Niedersachsen. Staerkung der Inanspruchnahme der U8/U9/J1

56. Matti Lehtinen. Preparations for implementing human papillomavirus vaccination should begin. Eurosurveillance weekly releases 2005. Vol. 10

57. Munoz N, Bosch FX, Castellsague X et al. Against which human papillomavirus types shall we vaccinate and screen ? The international perspective. Int. J. Cancer 2004;111:278-285

58. Bosch FX, Manos MM, Munoz N et al. Prevalance of Human Papillomavirus in Cervical Cancer : a Worldwide Perspective. J Natl Cancer Inst 1995;87:796-802

59. Koutsky LA, Ault KA, Wheeler CM et al. A controlled trial of a human papillomavirus type 16 vaccine. N Engl J Med. 2002;347:1645–51

60. Harper DM, Franco EL, Wheeler C et al. Efficacy of a bivalent L1 virus-like articlevaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomized controlled trial. Lancet 2004;364:1757-65

61. Villa LL, Costa RL, Petta CA 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 Oncol. 2005 May;6(5):271-8

62. Gardasil, Merck's investigational cervical cancer vaccine, produced high anti-HPV immune response in adolescents. Data presented at "The European Society of Pediatric Infectious Diseases (ESPID). Research & Development News: http://www.merck.com/

63. Poland GA, Jacobson RM, Koutsky LA et al. Immunogenecity and reactogencity of a novel vaccine for human papillomavirus 16: A 2 year randomized controlled clinical trial. Mayo Clin Proc. 2005;80(5):601-610

64. Olsson Sven-Eric. Primary prevention through vaccination: A new approach to cervical cancer. Abstract Book: Leading the fight against cervical cancer: Primary Prevention through Vaccination. Presented at the ECCO 13 Conference, Paris 30 Oct. – 3 Nov. 2005

65. Goldie SJ, Grima D, Kohli M et al. A comprehensive natural history model of HPV infection and cervical cancer to estimate the clinical impact of a prophylactic HPV-16/18 vaccine. Int. J. Cancer 2003;106:896-904

66. Sue J. Goldie. Chapter 15: Public Health Policy and Cost-Effectiveness Analysis. Journal of the National Cancer Institute Monographs No. 31, 2003

67. Gold MR, Siegel JE, Russell LB, Weinstein MC, editors. Costeffectiveness in health and medicine. New York (NY): Oxford University Press; 1996

68. Goldie SJ, Kohli M, Grima D et al. Projected Clinical Benefits and Cost-effectiveness of a Human Papillomavirus 16/18 Vaccine. J Natl Cancer Inst. 2004;96:604–15

69. Taira AV. Evaluating human papillomavirus vaccination programs. Emerg Infect Dis 2004;10:1915–1923

70. Gesundheitsbericht fuer Deutschland. Boesartige Neubildungen: 5.7 Zervixkarzinom. http://www.gbe-bund.de/pls/gbe

71. Petry KU, Hillemanns P, Germe M et al. Resource use and costs associated with the management of Pap III, Pap IIID and Pap IV in the pre-HPV vaccine era in Germany. Poster presented at the ECCO 13 conference, Paris; 30 Oct. – 3 Nov. 2005

72. Reiter S, Rasch G. Heft 1 – Schutzimpfungen aus der Reihe "Gesundheitsberichterstattung des Bundes". Robert Koch-Institut, Überarbeitete Neuauflage Januar 2004

73. Virushepatitis B, C und D: Situationsbericht im Jahr 2004. Robert Koch-Institut Epidemiologisches Bulletin Nr. 46: 18. November 2005

74. Hughes JP, Garnett GP, Koutsky L. The theoretical poplulation-level impact of a prophylactic Human Papilloma Virus Vaccine. Epidemilogy 2002;13:631-39

Eidesstattliche Erklärung

Ich versichere, dass ich die vorliegende Arbeit selbstständig verfasst und nur die angegebenen Quellen benutzt habe. Die Arbeit hat in dieser oder in ähnlicher Form noch keiner Prüfungsbehörde vorgelegen.

Statutory declaration

This is to declare that I have prepared this thesis by myself using only the sources mentioned. This thesis – or any variation thereof - has never been submitted to any examination authority.

28th February 2006

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Amena Ahmad