Human Papillomavirus

in

Ireland

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The Health Protection Surveillance Centre

Report prepared for Dr Darina O’Flanagan

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In September 2006, the journal Vaccine published a supplement entitled; HPV vaccines and Screening in Prevention of Cervical Cancer. Material from this publication has provided helpful insight, and commentary which has been used in the drafting of this document.

Our thanks also to Ms. Kirsty MacKenzie for her invaluable help in tracking down publications and reference material.

Foreword
Cervical cancer gives rise to considerable morbidity and mortality particularly in the least developed countries of the world. The disease gives rise to considerable distress and disability. As our understanding of the disease process has increased, we know that infection with human papillomavirus is a necessary part of the causal pathway.

The development and introduction of a vaccine designed to prevent the most prevalent high-risk HPV types is welcome. However, the complex interaction between viral particles and host, their genetic composition, and exposure to social, environmental, behavioural and cultural mores, collectively determine the natural history of HPV infection. What then is the impact on the incidence of cancer and our ability to screen effectively and treat those affected in a timely and acceptable manner? This document attempts to review our understanding of HPV and identify a framework for further analysis that can be used to guide vaccine policy development.
**Summary**

HPV infection is the most common sexually transmitted disease worldwide. The clinical spectrum of disease ranges from asymptomatic infection, to benign warts (primarily low risk types 6 and 11)\(^1\)\(^2\) to invasive malignancy\(^3\)\(^4\) (with over 70% of cervical cancer associated with the high risk genotypes 16 and 18\(^5\).)

Five years following the onset of sexual activity about 50% of young women will have been infected with at least one of the 40 HPV types that preferentially infect the genitals\(^6\). A total of thirteen of these HPV types are highly carcinogenic. Although there is a clear understanding of the epidemiology and pathogenesis of genital infection in women has developed over the past two decades, less is known about HPV infections in men. Studies suggest a similar infection pattern in men, who are the most important source of transmission of HPV disease to women\(^7\)\(^8\).

The peak incidence of HPV infection occurs in young adults between the ages of 16 and 23 years. An estimated 80% of all sexually active individuals have been infected with at least one serotype by age 50 years\(^9\). HPV prevalence is highest in 14-19 year olds. In the USA the percentage of females reporting ever being sexually active by age are 29% for 9th graders, 39% for 10th graders, 50% for 11th graders, and 60% for 12th graders.

Most HPV infections are asymptomatic and transient and will spontaneously resolve without treatment. Although 70% of new HPV infections clear within 1 year, and 91% clear within 2 years\(^2\)\(^10\), high risk types are more persistent than low risk types. Persistent infection over a number of years to decades may lead to grade 2 or 3 cervical intraepithelial neoplasia (CIN) and cervical cancer. Up to one percent of the young adult general population is actively infected with external genital warts at any time.

Primary prevention strategies include reduced exposure by changes in sexual practices (i.e. lifelong monogamy and use of condoms), and by vaccination\(^11\). Secondary prevention strategies include cervical cytology screening for early stage detection, HPV screening, and removal of HPV infected precancerous lesions by laser, cryosurgery, LEEP excision and cervical conization. In countries where there is an organized cervical cancer screening programme, there has been a marked reduction in the incidence of invasive cancer; however, screening and treatment has not been equally accessible to all groups of women\(^12\).

Recently a quadrivalent recombinant prophylactic vaccine against HPV has been licensed and a second bivalent vaccine’s licensure is imminent\(^13\). We are now in a position where decisions will need to be taken. These decisions relate to who and when to vaccinate, the choice of HPV vaccine, i.e. what disease to target (high
risk HPV alone or also external genital warts) and what level of vaccine penetration will be necessary to substantially reduce disease prevalence.
**Introduction/ Background**

During 2005 an expert group gathered to consider the implication of a vaccine designed to prevent adverse outcomes associated with high-risk Human Papillomavirus (HPV) in young women\(^{14}\).

The group identified a number of questions that a Minister of Health in a given country would seek to answer should he/she wish to implement a vaccination campaign. These questions are listed below (Figure 1).

**Figure 1 What a Minister of Health would want to know before introducing HPV vaccine\(^{14}\)**

1. What is the burden of disease related to HPV in their country, or in a country of similar demographic circumstances in the same region
2. What are population attitudes towards cervical cancer and HPV
3. What is the peak age of infection with HPV, and what are the implications for the choice of target age group?
4. What is the number of doses needed to generate adequate immunity through high risk period, and in particular, is it possible to use a two-dose vaccination schedule instead of a three-dose schedule?
5. Might HPV vaccination be integrated in the infant immunization schedule, or at school entry, at any time in the future, with or without a booster dose just before the high-risk period?
6. Can the vaccine be administered simultaneously with other vaccines such as those containing measles and rubella vaccines and tetanus toxoid?
7. What are the cold chain requirements for the vaccine?
8. What is the cost of the vaccine, and what are the potential mechanisms to finance this?

Echoing these questions, Lowndes et al raise a number of questions relating to the impact of vaccination on the health of the population that will need to be addressed by immunisation policy \(^{15}\).
This document will consider what we currently know about HPV, its natural history, epidemiology and consider the impact of HPV vaccines.

Data from Ireland are examined to determine the burden of disease and trends in incidence in recent years.
**HPV characterisation**

HPV are small, non-enveloped viruses that infect cutaneous and mucosal epithelial tissues. More than 100 types of HPV have been identified (Figure 3), of which more than 40 infect the genital tract, causing a variety of associated benign and malignant lesions\(^\text{16}\). Common cutaneous and plantar warts cause significant morbidity in both adults and children. Different HPV types have been identified by DNA analysis from HPV lesions commonly found in genital warts (condyloma acuminatum), respiratory papillomas, and other locations. HPV types, 16, 18, 31, 33, 35, 45, and 56 are high-risk types for anogenital malignancies. HPV 1 and 2 are found in plantar and common warts. HPV 5 and 8 are associated with skin cancer in patients afflicted with the rare hereditary skin diseases epidermodysplasia verruciformis.

**Classification**

Papillomaviruses are highly diverse and have a number of taxonomic levels; “family”, “genus”, “species”, “types”, “subtypes”, and variants\(^\text{16}\). HPV types are classified according to their nucleotide sequences (E6, E7 and L1 genes, this represents about a third of the genome) and form five major taxonomic groups (Alpha-Epsilon)\(^\text{17}\). These groups are not phenotypically homogenous. Two of these groups (Alpha and Beta) contain most of the HPVs.

*Figure 3 Phylogenetic tree containing the sequences of 118 papillomavirus types*\(^\text{16}\)
Genital HPV types have been separated into high and low risk groups according to the observed risk of malignant progression (Table 1). The distinction between high and low risk HPV types have been made primarily because clinical disease caused by infection with low risk HPV types are usually clinically benign and rarely progress to neoplasia. High risk HPV types are responsible for most high grade, precancerous lesions and >99.7% of cervical cancers

<table>
<thead>
<tr>
<th>Classification</th>
<th>HPV Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk or carcinogenic</td>
<td>16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59</td>
</tr>
<tr>
<td>Probably carcinogenic</td>
<td>26, 53, 66, 68, 73, 82</td>
</tr>
<tr>
<td>Low-risk</td>
<td>6,11, 40, 42, 43, 44, 54, 61, 70, 72, 81, 89</td>
</tr>
</tbody>
</table>
Natural History

The life cycle of HPV is dependent on active cellular replication and subsequent cellular division. Because the uppermost layers of the squamous epithelium have undergone terminal differentiation and are no longer dividing, HPV requires access to the undifferentiated basal layer of the epithelium to initiate a productive infection cycle (Figure 4).

Current hypothesis suggests that HPV accesses the underlying basal layer through naturally thin epithelial layers, such as those found in the transformation zones of the cervix or anus, or through micro-abrasions in the epithelium produced during sexual activity. Once infection has been established, the virus uses host cell machinery to replicate viral genetic material to express viral proteins. Because viral replication is dependent on continued cellular division, the virus has evolved to express proteins that inhibit cellular differentiation and stimulate continued cellular proliferation. Therefore unrestricted cell growth is
the hallmark of HPV infection, and many HPV associated clinical manifestations can be explained by these molecular mechanisms.

The structure of HPV is that of a non-enveloped virus, with a capsid enclosing a double-stranded circular DNA genome (Figure 6). It consists of early (E) and late (L) genes that are involved in transcription of non-structural early proteins and of the major capsid proteins.

Figure 5 Diagrammatic representation of the HPV virus and illustrates how Virus Like Particles (VLPs) arrange themselves to mimic the virus

There is no viraemia in the lifecycle of HPV. HPV can adhere to and enter several cell types, although its mode of entry into the cell and its translocation into the nucleus is not clearly understood. Expression of some of the early proteins E1 and E2 take place in the basal cells of the epithelium. In the para-basal cells there is transcription of E6 and E7 to permit subsequent HPV DNA replication

Pathogenesis
In the setting of cervical cancer, it is common for the viral genome to be integrated into the host genome that transforms the cell. This integration most often occurs around and with disruption in the E1/E2 transcription regulatory region of the virus, leading to an increased expression of the E6 and E7 oncogenes. The oncoproteins E6 and E7 impair the cell’s ability to repair
itself, leading to accumulation of cellular mutations. These gene products are expressed in all HPV-induced lesions and are required to maintain the proliferative state. Thus for a therapeutic vaccine to work, it will need to target E6 and E7 gene products.

The high risk types of HPV including HPV-16 and HPV-18 are preferentially involved in transforming and immortalising activities. These activities have been localised to the early proteins, E6 and E7, that interact with host proteins whose normal role is to regulate cell proliferation. Expression of E6 and E7 is necessary for keratinocyte immortalisation and for maintenance of the cancer phenotype. Thus an understanding of these proteins and methods to control their activity will be important to understand and control the carcinogenic potential of HPV.

Immunology
The immune system normally controls viral infections by neutralising antibodies produced by B cells (humoral immunity) or by the killing of virally infected cells by cytotoxic T cells (cell mediated immunity). Humoral immunity is important in protecting an individual from being infected but is not as important as cell mediated immunity in clearing the infection\(^20\)\(^21\). It is thought that in the majority of individuals infected with HPV a strong, local, cell-mediated immunity is induced. This results in clearance of HPV-induced lesions and protection against subsequent infection with the same HPV type\(^22\). In many infected individuals, serum antibodies are induced that are directed against conformational epitopes on the major viral capsid protein (L1) that is displayed on the outer surface of the virion. The L1 antibody responses occurring after natural infection are delayed and are present in low titres. This is thought to be due to the fact that the viral capsid proteins are only expressed in the upper layers of HPV infected epithelium and are not efficiently presented to the systemic immune system. Antibodies directed against L1 capsid proteins of a given HV type appear to neutralise that HPV in various \textit{in vitro} and \textit{in vivo} models\(^23\). Despite the low titres of neutralising antibody produced during natural infection, animal models indicate that neutralising antibody confers protection against subsequent infection, perhaps for life. It is unclear what proportion of naturally occurring immunity is mediated through humoral immunity and how much through cell-mediated immunity directed against structural and non-structural viral proteins\(^24\).

Type-specific neutralising antibodies are found in both regressing and progressing lesions, suggesting that these do not influence the regression process and that humoral immunity does not increase one’s susceptibility to the development of HPV lesions. In contrast, patients with altered CD4+ T cell
function, such as solid organ transplant recipients and those infected with HIV have an increased prevalence of HPV infection and related diseases such as cervical intraepithelial neoplasia (CIN)\textsuperscript{25}. Persistent infection results when cell-mediated immunity fails to clear the virus. It is persistent rather than transient HPV infection which has been shown to correlate with the development of dysplasia. The strategy of a prophylactic vaccine is to immunize individuals prior to viral exposure, to stimulate adequate neutralising antibody and to prevent initial infection. Antibody to the viral capsid proteins L1 and L2 can neutralise extracellular virus\textsuperscript{8}. Thus it would be important to have different arms of the immune system prepared to tackle HPV prevention versus HPV disease.

**Figure 6 Outline of the natural history of HPV**

Coexisting factors;
- Smoking
- Host (HLA, p53 polymorphism
- Oral contraceptive use
- Parity
- Other STDs
- Nutrition

Normal Cervix

Infection

HPV infected cervix

Persistence (>1 yr)

Progression

Pre-cancer

Cancer

Clearance

Regression

Mild Cytologic Abnormalities and/or Seroconversion
Cancer risk
Cervical cancer affects approximately 500,000 women worldwide each year\textsuperscript{26}. Most cases occur in less developed countries where effective screening programmes are not established. This is illustrated below (Figure 7, Figure 8);

Figure 7 Cervical Cancer Cases worldwide

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{cancer_cases_worldwide}
\caption{Cervical Cancer Cases worldwide}
\end{figure}

Figure 8 Cervical Cancer by Country 2002\textsuperscript{*}

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{cancer_cases_by_country}
\caption{Cervical Cancer by Country 2002\textsuperscript{*}}
\end{figure}

\textsuperscript{*}Figures are age-standardised

\textsuperscript{Source: Ferlay et al\textsuperscript{27}}
The disease is most commonly diagnosed in the fifth decade of life, contrasting with breast, lung and ovarian cancer which are diagnosed later in life. The median age of diagnosis in the USA is 47 years, nearly half of all cases are diagnosed before the age of 35. Women over the age of 55 years contribute disproportionately to cervical cancer mortality due to late presentation and advanced disease at the time of diagnosis.

The causal role of HPV in cervical cancer is supported by several arguments:

- Virtually all cervical cancers contain HPV DNA, usually of type 16, 18, 31, or 45;
- HPV mRNA has been detected in cervical cancer tissues, indicating that the HPV genome is expressed in these lesions;
- Infection with high risk HPV types precedes the development of CIN;
- The risk of developing CIN is 11 fold increased in those women with HPV type 16 and 18 compared to those without HPV DNA;
- Persistence of the HPV-16 is associated with a risk of cervical carcinoma in-situ, indicating that disappearance of the causal agent reduces the risk of disease.

The epidemiological evidence linking the “high-risk” or “carcinogenic” viruses with cervical cancer includes case series of women with cervical cancer. One of the largest of these series identified “high-risk” HPV-DNA in over 99% of approximately 1,000 invasive cervical cancers collected from 22 countries around the world. The distribution of HPV types associated with cervical cancer globally has been evaluated in a recent meta-analysis including approximately 10,000 cases. The eight most common HPV types detected in descending order of frequency are: HPV 16, 18, 45, 31, 33, 52, 58, and 35. These eight types of HPV are responsible for 90% of all cervical cancers world-wide. Further evidence from case-control studies that allow the estimation of the relative risk linked to each individual HPV type. The largest of these studies pooled data from 11 case-controlled studies from different countries that used the same methodology to test for HPV. It included about 2,500 women with cervical cancer and 2,500 control women and reported extraordinary high odds ratios for infections with “high-risk” types of HPV (Figure 9).
Figure 9 Type-specific odds ratios (OR) and 95% confidence Intervals (CI) for cervical carcinoma (squamous-cell and adenocarcinoma)*

*Subjects with HPV-DNA negative results were used as the reference category. ORs are adjusted by country and age-group. HR= “high-risk”, LR= “low-risk”. HPV X denotes undetermined type.

HPV 16 and -18 are the two most common types found in association with either squamous cell carcinomas or adenocarcinomas. The fraction of squamous cell carcinomas or adenocarcinomas attributable to HPV 16 or -18 was 70% and 86% respectively.

The causative role of certain HPV types in cancer was reviewed in an evaluation at the International Agency for Research on Cancer (IARC) in February 2005 (Table 2). The evidence of causality of HPV in cervical cancer is such that the Agency has acknowledged “high risk” HPV as a human carcinogen.
Table 2 Papillomavirus types involved in different human cancers

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Papillomavirus types involved</th>
<th>Percentage of cases HPV-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 (26, 68, 73, 82)</td>
<td>&gt;95</td>
</tr>
<tr>
<td>Vulval: Basaloid</td>
<td>16, 18</td>
<td>&gt;50</td>
</tr>
<tr>
<td></td>
<td>Warty</td>
<td>&gt;50</td>
</tr>
<tr>
<td></td>
<td>Keratinizing</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Vulval: Warty</td>
<td>16, 18</td>
<td>&gt;50</td>
</tr>
<tr>
<td></td>
<td>Warty</td>
<td>&gt;50</td>
</tr>
<tr>
<td></td>
<td>Keratinizing</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Penile: Basaloid</td>
<td>16, 18</td>
<td>&gt;50</td>
</tr>
<tr>
<td></td>
<td>Warty</td>
<td>&gt;50</td>
</tr>
<tr>
<td></td>
<td>Keratinizing</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Vaginal</td>
<td>16, 18</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Anal</td>
<td>16, 18</td>
<td>&gt;70</td>
</tr>
<tr>
<td>Oral cavity and tonsils</td>
<td>16, 18, 33</td>
<td>~25</td>
</tr>
<tr>
<td>Nail bed</td>
<td>16</td>
<td>~75</td>
</tr>
</tbody>
</table>

The consensus was that there is sufficient evidence for carcinogenicity of the anogenital tract for types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 (the “high-risk” types of HPV). Some case control studies also point to a role of HPVs 26, 68, 73, 82 in cervical cancer, but they are found relatively rarely14.

Infection with high risk HPV appears to be necessary for the development of cervical cancer, but it is not necessarily a sufficient condition. Several co-factors are suspected to play an important role in the development of cervical cancer. They include multiparity, tobacco smoking, long term usage of oral contraceptives, cervical inflammation, especially when it is associated with Chlamydia trachomatis or HSV co-infection, antioxidant nutrients, and immunosuppression. A history of previous genital warts is associated with an increased risk of cervical HPV infection10 32-38.

A systematic review of cervical cancer and the use of hormonal contraceptives found an increase in risk with increasing duration of use, but more data are needed on the extent to which the observed associations remain after use of hormonal contraceptives has ceased39. There is no convincing evidence that condom use reduces the risk of HPV infection. Some studies show a reduction in risk for genital warts, moderate or high-grade cervical intra-epithelial neoplasia (CIN 2 or 3) or cervical cancer, but no data on protection against endpoints are consistent36. Circumcision may be associated with reduced transmission.

Other HPV-related cancers in young women include vulvar and vaginal cancers, which are preceded by dysplastic lesions (vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia VaIN)40 41. In men anal cancer is the most common HPV related cancer42 43. The virus is also related to penile and certain oropharyngeal cancers44. Other benign HPV-associated conditions include condyloma acuminate (genital warts) located in the genital or perianal region and juvenile recurrent respiratory papillomatosis primarily located in the larynx45.
The global epidemiology of HPV and cervical cancer suggest that the majority of cervical cancers are related to two types HPV 16, around 55%, and HPV 18, around 15% (Figure 10). The contributions of HPV 16 and HPV 18 to high-grade CIN and to HPV related vulvar, vaginal and anal cancers are similar to those found in cervical cancer. HPV 6, 11, 16, and 18 together cause about 35% of CIN-1 cases. HPV 6 and HPV 11 cause approximately 90% of genital warts and 10% to 20% of CIN-1 lesions, respectively, but are not associated with cervical or anal carcinoma.

Figure 10 Percentage and numbers of cervical cancer cases attributed to the most frequent HPV genotypes in all world regions combined (women 15 years of age and older)

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Percentage</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV16</td>
<td>53.5%</td>
<td>251,191</td>
</tr>
<tr>
<td>HPV18</td>
<td>17.2%</td>
<td>80,859</td>
</tr>
<tr>
<td>HPV45</td>
<td>6.7%</td>
<td>31,549</td>
</tr>
<tr>
<td>HPV31</td>
<td>2.9%</td>
<td>13,678</td>
</tr>
<tr>
<td>HPV33</td>
<td>2.6%</td>
<td>12,134</td>
</tr>
<tr>
<td>HPV52</td>
<td>2.3%</td>
<td>10,929</td>
</tr>
<tr>
<td>HPV58</td>
<td>2.2%</td>
<td>10,242</td>
</tr>
<tr>
<td>HPV35</td>
<td>1.4%</td>
<td>6,570</td>
</tr>
<tr>
<td>HPV59</td>
<td>1.3%</td>
<td>6,137</td>
</tr>
<tr>
<td>HPV56</td>
<td>1.2%</td>
<td>5,769</td>
</tr>
<tr>
<td>HPV51</td>
<td>1.0%</td>
<td>4,641</td>
</tr>
<tr>
<td>HPV39</td>
<td>0.7%</td>
<td>3,211</td>
</tr>
<tr>
<td>HPV68</td>
<td>0.6%</td>
<td>2,714</td>
</tr>
<tr>
<td>HPV73</td>
<td>0.5%</td>
<td>2,339</td>
</tr>
<tr>
<td>HPV82</td>
<td>0.3%</td>
<td>1,350</td>
</tr>
<tr>
<td>Other</td>
<td>1.2%</td>
<td>5,630</td>
</tr>
<tr>
<td>HPV X</td>
<td>4.4%</td>
<td>20,769</td>
</tr>
</tbody>
</table>

Source: Muñoz et al.
Epidemiology/ Human Studies
Although clinical HPV infections are the most recognizable and most important for the patient and practitioner, sub-clinical and asymptomatic (latent) infections are probably most common. An estimated 80% of all sexually active individuals have been infected with at least one serotype by age 50 years. USA studies reveal highest HPV prevalence in 14-19 year olds. The percentage of females reporting ever being sexually active by age are 29% for 9th graders, 39% for 10th graders, 50% for 11th graders, and 60% for 12th graders (Table 3).

Table 3 Proportion of female High School students reporting sexual activity

<table>
<thead>
<tr>
<th>Grade (14-18 years)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>9th</td>
<td>29</td>
</tr>
<tr>
<td>10th</td>
<td>39</td>
</tr>
<tr>
<td>11th</td>
<td>50</td>
</tr>
<tr>
<td>12th</td>
<td>60</td>
</tr>
</tbody>
</table>

In a cohort study of Columbian women, the age specific incidence of infection with “high-risk” types was found to be highest in the late teens and 20s with a second peak in middle age.

Figure 11 Incidence rate of Human Papillomavirus (HPV) infection by age among cytologically normal women in Botota, Colombia, 1993-2001*

* Upper line relates to all HPV types, while the lower line relates to “high-risk” types.

Most HPV infections are asymptomatic and transient. Although about 70% of new HPV infections clear within 1 year and about 91% clear within 2 years, high
risk types are more persistent than low risk types\textsuperscript{6,49,50}. Persistent infection with the same “high-risk” type is considered to be a predictor for moderate or high-grade intraepithelial neoplasia (CIN) and thus an intermediary step on the causal pathway to cancer\textsuperscript{14}.

In some studies at least one percent of the general young adult population are actively infected with external genital warts at any time\textsuperscript{51,52}.

**Figure 12 Persistence of Human Papillomavirus (HPV) by age group**

![Persistence of Human Papillomavirus (HPV) by age group](Source: Castle et al\textsuperscript{53})

IARC is collecting data on the distribution of HPV types in women with normal cervical cytology, through cross-sectional surveys in 15 countries. Low-risk, intermediate-risk and high-risk areas are represented, and each survey includes approximately 1000 women with 100 women per 5-year age group between 15 and 65+ years. Overall HPV prevalence varies 20-fold, from 1.4\% in Barcelona, Spain, and 1.6\% in Hanoi, Viet Nam, to 25.6\% in Nigeria. This correlates with the incidence of cervical cancer\textsuperscript{14}. 

20
Screening for cervical cancer
By identifying and treating cervical intraepithelial neoplasia (CIN), the cervical cancer precursor lesion associated with HPV infection, screening programmes based on cytology have reduced the incidence of invasive cervical cancer\textsuperscript{54}.

Smear testing
The Pap smear is an essential tool for the screening and prevention of cervical cancer\textsuperscript{55-57}. During the time from infection to the development of cervical cancer, several cytopathological stages (from mild to severe dysplasia) are recognized. The detection of these stages are identified with conventional Pap smears or liquid based cytology (LBC) tests which form the basis of cervical screening programmes\textsuperscript{58-61}. These programmes provide an early warning of abnormal cell development. Most low-grade cervical lesions are found and treated or removed with a high likelihood of preventing progression to cancer. Guidelines have been established on a consensus basis in a number of countries on timing of initial pap smear, follow up for those found negative and for those found positive (abnormal smear test). In countries where there is an organized cervical cancer screening programme, there has been a marked reduction in the incidence of invasive cancer; however, screening and treatment has not been equally accessible to all groups of women.

If one looks at the causes of cervical cancer screening failures in the US, it is clear that more than 50% of patients in whom cervical cancer develops have never been screened, and another 10 to 20% of those patients have not been screened for at least 5 years. However, at least 30% of the patients in whom cervical cancer develops have had a ‘false negative’ Pap smear and approximately half of those false negative results are due to sampling error while the remaining 50% actually are screening or interpretive errors\textsuperscript{62 63}. Any single cervical cancer screening programme may only be 50% sensitive for prevalent disease\textsuperscript{57 64}. Thus it is only through the repetitive application of independent screening events, at relatively short intervals, that the Pap smear system is really efficacious. While it is possible for women who routinely have perfect annual screening attendance to have very low rates of cervical cancer, even with perfect attendance, the system is imperfect and false negative results will continue to occur.

A more recent development in the area is that of thin layer cytology which has been widely implemented in many settings and increases the sensitivity and specificity of testing.
**HPV type testing**

While Pap smear testing has become the norm in most countries, the recent availability of HPV type testing has added complexity to the field. HPV DNA testing and typing may add substantially to a robust screening programme and in the USA guidance for the use of this test as a secondary prevention strategy, with or without Pap testing, has been developed\(^{58,65}\).

In a study by Dr Jack Cuzick et al from London\(^{66}\), colleagues analysed data from all European and North American studies that included routine cytology and additional HPV testing as a parallel test\(^{65,66}\). HPV testing was 96.1% sensitive in detecting cervical intraepithelial neoplasia (CIN 2+), compared with just 53% for cytology. By contrast, HPV testing had a lower specificity: 90.7% vs 96.3% for cytology. Smear testing was subject to variations with the location of where it was done as well as to patient age, while there was no such finding with HPV testing.

Many would argue that HPV testing could replace Pap smear testing, or significantly reduce its use in many situations. Several epidemiological studies have looked at the prevalence of HPV detection by age and have demonstrated that there is a significant reduction in HPV prevalence through the third decade, such that women in their 30s routinely show prevalence of detectable HPV of 10% or less\(^{67,68}\). Therefore, an extremely sensitive HPV test could effectively eliminate 80-90% of screened women from being considered at risk for cervical cancer\(^{58,69}\).

In summary, HPV testing has been shown to be more sensitive than cytology, is more reproducible than cytology, and, because of the high sensitivity of combined testing, the consequently high negative predictive value in a low prevalence population provides for less frequent screening, which ultimately may increase the compliance of patients with screening recommendations.

**Cost of HPV related disease**

A number of costing analyses have been done internationally. Annual health care costs that are associated with cervical HPV related diseases are sizable compared with US estimates for other sexually transmitted diseases\(^{70}\). In 1998, cervical disease accounted for total health care costs of $3.4 billion, with $60 million for hepatitis B, $1.8 billion for genital herpes, and $2 billion for Chlamydia. Estimates of the total economic burden of cervical HPV related disease would be even higher if one were to include indirect and non-medical costs (lost work and leisure time).

A study of Kaiser Permanente patients in California examined the health care costs of cervical HPV related disease in a US health care setting\(^{71}\). The study found that the annual cervical cancer prevention and treatment costs were
$26,415 per 1000 female enrollees, with routine cervical cancer screening accounting for expenditures of $16,746 per 1000 female enrollees, CIN accounting for expenditures of $4535 per 1000 female enrollee, cervical cancer accounting for expenditures of $2629 per 1000 female enrollees, and false-positive test results accounting for expenditures of $2394 per 1000 female enrollees (Table 4).

Table 4 Annual cost of preventing cervical cancer per 1,000 women enrolled

<table>
<thead>
<tr>
<th>Item of expenditure</th>
<th>Annual cost ($) per 1,000 women enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical cancer screening</td>
<td>16,746</td>
</tr>
<tr>
<td>CIN</td>
<td>4,535</td>
</tr>
<tr>
<td>Cervical Cancer</td>
<td>2,629</td>
</tr>
<tr>
<td>False positive results</td>
<td>2,394</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>26,415</strong></td>
</tr>
</tbody>
</table>

This translates into routine cervical cancer screening comprising 67%, with 10% of expenditures dedicated to the treatment of invasive cervical cancer, 17% to the management of cervical pre-cancers, and 9% dealing with false positive Pap smear test results.

Costing studies have been done in the UK NHS programmes including the cost of genital wart management additionally to those of cervical cancer prevention and treatment programmes. Costs they included as being associated with HPV infection were:
- cervical cytology;
- management of low and high grade lesions;
- treatment of cervical cancer, and;
- expenditure related to follow-up of false positive Pap tests results.

Although the setting and health care costs associated with treatment can vary, one study has reported that routine Pap tests costs about $60, and management of low and high grade lesions costs $1026 and $3235, respectively. If indirect costs associated with cervical cancer screening and follow up of abnormal Pap test results are included, these estimates will increase substantially.

Although genital warts are clinically benign, they are a significant cause of morbidity in affected men and women. HPV types 6 and 11, the two most common disease causing low risk HPV types, are responsible for 97% of genital wart manifestations. Current estimates suggest that >1% of all sexually active populations have genital warts. Treatment modalities are frequently painful, involve excisional desiccation of the lesion and usually require multiple treatments to be effective. Indeed up to 75% of treated genital warts recur within 6 months of treatment. Costs associated with treatment are very variable.
The cost of complete clearance is as follows; surgical excision, $285; cryotherapy, $951; and Interferon treatment is the most expensive at $6,665. This research estimated that the combined NHS related costs of cervical cancer care, screening and management of cervical and genital warts for 2003 was £208 million, ranging from £186.9 to £214 million based on sensitivity analyses.
**HPV vaccines**

Prophylactic HPV vaccines are formulations of the major capsid protein, L1, of the natural HPV particle. When L1 is expressed in a heterologous system, such as yeast, insect or mammalian cells, L1 monomers self-assemble into virus like particles (VLPs), which closely mimic the structure of natural HPV virions (Figure 5, p11). Studies in both animals and humans have shown that formulations of VLPs are nontoxic and contain no infectious genetic material. Because VLPs are recombinant proteins, VLPs have no oncogenic or disease-causing potential and are thus ideal candidates for use as vaccines. In addition it has been found that administration of VLPs in animals and humans generate neutralizing antibodies that bind to natural HPV virions preventing their entry into cells.

A controlled trial of a human papillomavirus type 16 vaccine, a prophylactic vaccine to prevent HPV infection, was one of the landmark studies to demonstrate the efficacy of such an approach.

Subsequently two vaccine manufactures have completed randomized controlled trials of their respective HPV vaccines. Their vaccine strategy has been to utilize, as described above, empty viral capsids called ‘virus like particles’ which can be synthesized and are immunogenic.

It is important to note that the end points used to determine efficacy were cervical intraepithelial neoplasia 2 and 3. In other words, surrogate markers were used rather than cervical cancer (Figure 13)

**Figure 13 Natural history of HPV infection, highlighting the surrogate markers chosen to determine vaccine efficacy**

- **0 to 1 Year**
  - Initial HPV Infection
  - CIN 1
  - Cleared HPV Infection
- **0 to 5 Years**
  - Continuing Infection
  - CIN 2/3
- **Up to 20 Years**
  - Cervical Cancer

Source: Courtesy of Soldan, K. HPA 2006
Phase I to III trials of the HPV vaccines

Data from completed and ongoing Phase III trials of the quadrivalent and bivalent vaccines suggest that safety of both vaccines has been excellent.

In five clinical trials that included 5088 women 9–26 years of age who were administered the quadrivalent vaccine, only 0.1% of the vaccine recipients discontinued due to adverse experiences. Vaccine recipients more frequently experienced injection site discomfort compared to placebo, but most vaccine recipients judged the injection site discomfort as mild to moderate. Slightly more vaccine recipients experienced fever (10.3%) 1–15 days post vaccination compared to placebo recipients (8.6%).

Both the bivalent and quadrivalent HPV vaccines have demonstrated truly remarkable efficacy in the Phase II and Phase III trials. The quadrivalent vaccine has been studied in three clinical trials, Protocol 007, Females United To Unilaterally Reduce Endo/ectocervical disease (FUTURE) I, and FUTURE II, Table 5.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>Median follow-up</th>
<th>Cases in vaccine recipients</th>
<th>Efficacy (%)</th>
<th>95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent infection with HPV-6, 11, 16 or 18</td>
<td>Protocol 007</td>
<td>235</td>
<td>3.0</td>
<td>4</td>
<td>233</td>
</tr>
<tr>
<td>HPV-16 or HPV-18 associated CIN-2,3 and AIS</td>
<td>Protocol 007</td>
<td>231</td>
<td>3.0</td>
<td>0</td>
<td>230</td>
</tr>
<tr>
<td>FUTURE I</td>
<td>2,200</td>
<td>2.4</td>
<td>0</td>
<td>2,222</td>
<td>9</td>
</tr>
<tr>
<td>FUTURE II</td>
<td>5,301</td>
<td>2.0</td>
<td>0</td>
<td>5,258</td>
<td>21</td>
</tr>
<tr>
<td>Combined</td>
<td>7,732</td>
<td>0</td>
<td>7,701</td>
<td>53</td>
<td>100</td>
</tr>
<tr>
<td>HPV-6, 11, or 18 associated genital warts</td>
<td>Protocol 007</td>
<td>235</td>
<td>3.0</td>
<td>0</td>
<td>233</td>
</tr>
<tr>
<td>FUTURE I</td>
<td>2,261</td>
<td>2.4</td>
<td>0</td>
<td>2,279</td>
<td>29</td>
</tr>
<tr>
<td>FUTURE II</td>
<td>5,401</td>
<td>2.0</td>
<td>1</td>
<td>5,387</td>
<td>59</td>
</tr>
<tr>
<td>Combined</td>
<td>7,897</td>
<td>1</td>
<td>7,899</td>
<td>91</td>
<td>99</td>
</tr>
</tbody>
</table>

In these trials the “per-protocol-population” (PPP) was defined as women who were:
- naive to the HPV types included in the vaccine through 6 months after entry;
- received all three vaccinations, and;
- had no significant protocol deviations.

In the “per-protocol-population”, persistent infection with the HPV types included in the vaccines was reduced by 89% in Protocol 007, (Table 5). CIN-2/3 and adenocarcinoma in-situ (AIS) associated with HPV 16, 18, were reduced by

Source: Wright et al.
100% in vaccine recipients compared to placebo recipients in all three trials, (Table 5).

Similarly, biopsy-confirmed genital warts associated with HPV-6, -11, -16, -18 were reduced by 100% in vaccine recipients compared to placebo recipients in Protocol 007 and FUTURE I, and by 98% in FUTURE II. The Phase II trial of the bivalent HPV-16/18 vaccine was divided into an initial follow-up period that had a median follow-up of 2.2 years and a subsequent follow-on study of a subset of the original enrollees with a median follow-up of 4.0 years76 77. In both study periods persistent infection with HPV-16 or -18 was reduced in the “per-protocol-population” by 100% in vaccine recipients compared to placebo recipients (Table 6).

**Table 6 Efficacy of bivalent HPV vaccine**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>Median follow-up</th>
<th>Cases in vaccine recipients</th>
<th>Number</th>
<th>Cases in placebo recipients</th>
<th>Efficacy (%)</th>
<th>95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent infection with HPV-16 or 18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harper et al77</td>
<td>366</td>
<td>2.2</td>
<td>0</td>
<td>355</td>
<td>7</td>
<td>100</td>
<td>77-100</td>
</tr>
<tr>
<td>Harper et al76</td>
<td>311</td>
<td>4.0</td>
<td>0</td>
<td>295</td>
<td>7</td>
<td>100</td>
<td>34-100</td>
</tr>
<tr>
<td>HPV-16 or HPV-18 associated CIN-2,3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harper et al76</td>
<td>481</td>
<td>2-4</td>
<td>0</td>
<td>385</td>
<td>5</td>
<td>100</td>
<td>-7.7-100</td>
</tr>
</tbody>
</table>

Source: Wright et al 31

In order to evaluate efficacy of the bivalent vaccine for reducing HPV-16 or -18 associated CIN-2/3, data from both follow-up periods were combined. After 2 and 4 years of follow-up, biopsy-confirmed CIN-2/3 associated with HPV-16 or -18 was reduced by 100% in vaccine recipients compared to placebo recipients.

Recently it has been shown that women vaccinated with the bivalent HPV vaccine show cross-protection against incident infection with HPV types 45 and 3176. Women who were vaccinated with the HPV-16 or -18 vaccine had a 94% (95% CI 63–100%) reduction in incident infections with HPV-45 and a 55% (95% CI: 12–78%) reduction in incident infections with HPV 31, compared to placebo recipients.

The vaccine products
Both Merck (using HPV 6, 11, 16, 18 antigens) and GlaxoSmithKline (using HPV 16, 18 antigens) have developed such vaccines and they have an excellent safety and immunogenicity profile. Both used a three-dose schedule consisting of an initial dose, a 2nd dose 1 month later, and a 3rd dose 6 months after the initial dose. The long term protection afforded by vaccination is not yet known due to relatively recent development of the HPV vaccines.
The currently licensed agent is Gardasil, manufactured and licensed by Merck and Sanofi-Aventis. The approval indications for Gardasil are as follows: Gardasil is a vaccine for the prevention of high grade cervical dysplasia (CIN 2/3), cervical carcinoma, high grade vulvar dysplastic lesions (VIN 2/3), and external genital warts (condyloma acuminata) causally related to HPV types 6, 11, 16, 18. The indication is based on the demonstration of efficacy of Gardasil in 9 to 15 year old children and adolescents. Protective efficacy has not been evaluated in males.’

The soon to be licensed GSK vaccine, Cervarix, has demonstrated efficacy against HPV types 16 and 18, the antigens present in its vaccine.

Vaccine effectiveness
Although the evidence demonstrates a high level of efficacy and safety, it is likely to be decades before we will be able to evaluate the impact of HPV vaccination on the incidence of cervical cancer using empirical data alone. A number of factors need to be considered and these will vary from setting to setting, such as the incidence of cervical cancer, temporal patterns in sexual behavior and parity, presence of ongoing cytology screening, and resources available for investments in health. It is difficult to determine the impact of vaccination in a given setting using empirical data alone. Mathematical models that integrate biologic, epidemiologic, economic, and behavioral data offer a quantitative and systematic approach to predicting the impact of HPV vaccination in different settings. Modelling has been used to identify those variables that may have the greatest impact on the cost and benefits associated with vaccination, as well as suggest potential strategies for incorporating an effective vaccine into existing screening programmes. Several well validated models of the natural history of cervical cancer have been developed and used to evaluate various screening strategies. Consistent themes have emerged from use of these models.

First, as screening frequency increases, the cost-effectiveness ratios increase dramatically due to increased detection of transient cervical abnormalities and associated low-grade CIN lesions. These transient lesions are primarily observed in younger women, which explains the second consistent finding; delaying screening until the mid-30’s is a more efficient strategy for reducing cancer mortality. In addition, screening appears to be less effective against rapidly progressing cancers, with proportionately smaller reductions in cancer incidence in younger women compared with women in their 40’s and 50’s. These findings suggest that the cost of HPV vaccination might be partly offset by saving achieved by delaying the age of beginning screening and by screening less frequently.
Sue J Goldie et al has developed a mathematical model to assess the relative costs and benefits of alternative policies (i.e. screening and/or vaccination) in reducing mortality from cervical cancer. They found that a prophylactic vaccine that prevents at least 70% of persistent HPV 16/18 infections should be able to substantially reduce HPV 16/18 associated SIL and cervical cancer, even in the setting of established cytology screening. They concluded that a combined programme of vaccination and screening that permits a later age of screening initiation and less frequent screening interval will likely be the most cost effective use of limited health care resources. They also commented that the overall vaccine effectiveness based on any analysis is dependent on providing adequate protection during the ages of peak oncogenic HPV incidence. Age of vaccination, HPV types covered, vaccine efficacy, and duration of efficacy are the specific components that determine such protection.

The availability of a vaccine will not lead to overnight changes in screening policy; a majority of older women will not be eligible for a vaccine, and uncertainty about issues that impact overall effectiveness, such as vaccine duration and replacement, is unlikely to be resolved prior to commercial availability.

Vaccine Cost effectiveness
In California, Taira et al developed disease transmission models that estimated HPV prevalence and infection rates for the population overall, by age group, by level of sexual activity within each age group, and by sex. Data were based on clinical trials and published and unpublished sources. They calculated that an HPV-16/18 vaccine for 12 year old girls would reduce cohort cervical cancer cases by 61.8%, with a cost effectiveness ratio of $14,583 per quality-adjusted life year (QALY). Including male participants in a vaccine rollout would further reduce cervical cancer cases by 2.2% at an incremental cost effectiveness ratio of $442,039/QALY compared to female only vaccination.

In summary, using a disease transmission model for the sexual transmission of HPV, they demonstrated that an HPV-16/18 vaccine would be cost effective and would reduce lifetime cervical cancer cases by 61.8%. Although a universal vaccination programme would have greatest benefit, because of the benefits of herd immunity, even a programme that achieves 70% coverage would dramatically reduce cohort lifetime cervical cancer rates. They also demonstrated that vaccinating women at the onset of sexual activity would be cost effective and lead to the greatest reduction in cervical cancer incidence. Thus focusing on vaccinating at the age of 12 would be the most cost effective, assuming that a booster vaccine may be required at 10 year intervals.
The National Immunisation Advisory Committee (NIAC) is now in a position to consider who and when to vaccinate with a HPV vaccine and what level of vaccine penetration will be necessary to substantially reduce disease prevalence.

A first question will be whether both sexes should be vaccinated. Although the long-term sequelae of HPV for men is on average less serious.

Unresolved Issues

Important issues requiring careful consideration prior to the introduction of a prophylactic HPV vaccine include:

- What age groups should be targeted;
- Whether males and females both should be targeted;
- The durability of the immune response;
- The implications for cervical cancer screening programmes, and;
- The proportion of attributable disease to the HPV types targeted by the available vaccines

Target populations

*Optimal age groups for vaccination*

The optimal target populations for the HPV vaccines have not yet been clearly defined and are likely to vary from country to country because of differences in age at first intercourse/exposure to HPV, epidemiology, and available vaccination platforms. Both HPV vaccines prevent persistent infections and the development of HPV-associated lesions due to the vaccine HPV types in women 15–26 years of age who are both HPV-DNA and serologically negative for the vaccine HPV types. Immunological “bridging studies” have documented better serological responses to the quadrivalent vaccine among 9–15 year old females than among older adolescents and women. Based on this, the U.S. FDA recently approved the quadrivalent vaccine for use in women 9–26 years of age. The two HPV vaccines under consideration are considered “prophylactic” rather than “therapeutic” vaccines and optimally should be administered prior to natural exposure to the vaccine HPV types. HPV infections are both extremely common and readily transmitted between sexually active adolescents and young adults. The majority of females become infected with at least one type of HPV within 2–5 years of initiating sexual activity. Since HPV 16 and 18 are among the most common HPV types found in adolescents and young adults, maximum benefit will be achieved by vaccinating prior to initiating sexually activity. The age at which girls initiate sexual activity varies considerably between different countries and cultures.
Other age groups for vaccination
If only 9–13 year old females are targeted for vaccination it will take 20 years before any impact of the HPV vaccine on cervical cancer is observed. Full effects of vaccination on cervical cancer would likely take 30 or 40 years. This may be too long for many countries, which will want to introduce “catch-up” vaccination for sexually-active females. There are a number of issues that need to be taken into account when considering vaccination of sexually-active women. One is whether these women will benefit from vaccination. Although the HPV vaccines have already been demonstrated to be effective in sexually-active females 15–26 years of age, to date, benefit has only been documented for women who are HPV-DNA negative and serologically negative for the vaccine HPV types. Thus, older, sexually-active women who have been infected with one or more of the vaccine types of HPV may either not benefit, or have a reduced benefit, from vaccination. It is important to note that vaccination of women already naturally infected with vaccine HPV types has not been associated with any adverse effects in the clinical trials.

Vaccination of sexually-active women raises another issue; should pre-vaccination testing for HPV be performed. It is unlikely that pre-vaccination testing for HPV will provide clinically useful information since neither HPV serological assays nor HPV-DNA tests are good measures of infection with HPV. Approximately one-half of HPV-infected individuals remain serologically negative and the detection threshold of commercially-available HPV-DNA tests has been adjusted to identify women with cervical neoplasia, rather than women who are infected with HPV. After considering all of these issues, the U.S. Advisory Committee on Immunization Practices (ACIP) recently recommended that even though the primary target population is females 11–12 years old, sexually active females 13–26 years old should also be vaccinated in the U.S.

Vaccination of males
Although encouraging immunogenicity trials of the HPV vaccines in males have been conducted, to date there is no data documenting efficacy. If efficacious in males, there may be considerable interest in some industrialized countries in vaccinating adolescent males with the quadrivalent vaccine in order to reduce risk for anogenital warts. There is less of a compelling argument for vaccinating males with the bivalent HPV 16, 18 vaccine. Even though the burden of HPV 16 and 18 associated penile, anal, and oropharyngeal cancers in males is not insignificant, it is considerably less than the burden of HPV 16 and 18 associated cervical disease in women.

Mathematical models can also be used to evaluate the incremental benefits and cost-effectiveness of vaccinating males. In contrast to vaccinating against
common childhood infectious diseases, vaccinating against a sexually transmitted disease requires consideration of the heterogeneity in risk and the nature of contacts between men and women\textsuperscript{82}. The value of vaccinating both men and women depends upon how well vaccinating women alone controls the spread of infection. With moderate heterogeneity in risk behaviour and high vaccination coverage of women, the benefits of vaccinating men is predicted to be limited for the purpose of cervical prevention\textsuperscript{85}, and may not be cost-effective. Herd immunity effects of vaccination can protect unvaccinated individuals in the population, but are only fully protective at high levels of vaccination coverage. Even at high levels of coverage, the existence of high-risk groups can make elimination of the disease difficult and lead to diminishing returns of increased vaccination coverage.

Need for Boosters
The durability of the immune response engendered by the HPV vaccines is unknown. Both a mono-valent HPV 16 vaccine and the bivalent HPV-16/18 vaccine result in levels of neutralizing antibodies that are considerably higher than those encountered after natural infection. In addition, the antibody responses that are produced through vaccination appear to be quite durable, lasting for at least 42 months\textsuperscript{23, 76}. Over the next several decades it will be important to monitor antibody levels and HPV infections in immunized subjects to determine whether boosters will be needed and if so, how many years after vaccination.

Impact of vaccination on screening programs
Even after vaccination programs have been instituted and reasonable levels of coverage obtained, cervical cancer screening programs cannot be discontinued. There are a number of reasons why screening will need to continue for the foreseeable future. One is that the primary target population for vaccination is 9–13 year old females. Although some “catch-up” vaccination of older, sexually active women will occur in many countries, much lower rates of coverage will likely be achieved though “catch-up” vaccination efforts compared to a targeted cohort vaccination of young adolescents. Another reason why screening programs have to be maintained is that vaccination will not protect, against the HPV types not included in the vaccines. Depending on geographic location, HPV 16 and 18 account for only 62% to 77% of all cervical cancers\textsuperscript{30}. In addition, although a dramatic 100% protection against HPV 16 and 18 associated CIN-2/3 was observed in the Phase II and Phase III trials of the HPV vaccines, it is very likely that with longer follow-up protection will begin to decline. Although there may be some cross-protection against other “high-risk” types of HPV achieved by
vaccinating against HPV 16 and 18, the extent and duration of cross-protection is currently unclear.

Given that screening will need to continue after the introduction of HPV vaccination programs it will be important to re-evaluate how we screen. It is likely that the current approach of frequent screening utilizing cytology will prove to be too expensive and inefficient for many countries. Most countries that introduce HPV vaccination will eventually want to switch to HPV-DNA testing as the primary screening test since not only does it have better performance characteristics than cervical cytology, but using HPV testing for screening coupled with HPV genotyping will provide a simple strategy to monitor long-term protection among vaccinated women. HPV testing systems amenable to use in areas with limited health infrastructures are currently being developed and evaluated.

Proportion of attributable disease
The burden of disease attributed to HPV in Ireland is considered in the following section.
HPV in Ireland

Ano-genital Warts
Clinical diagnoses of ano-genital warts are notifiable. Surveillance data generated by clinical notifications indicate a rising trend in the number of new infections each year. Figure 14 illustrates the rising trend since 1989.

Figure 14 Rate of clinical notifications of ano-genital warts in Ireland 1989 to 2005.

The rise in notifications is equal among men and women. Young adults aged 20-29 years account for a large proportion of disease. This is outlines in Figure 15 and Figure 16 below.
Figure 15 Total number of ano-genital wart notifications by sex in Ireland; 1995 - 2005

![Graph showing total number of ano-genital wart notifications by sex in Ireland (1995-2005).](image)

Source: Health Protection Surveillance Centre

Figure 16 Age profile of those notified with ano-genital warts in Ireland 1996-2005

![Graph showing age profile of ano-genital wart notifications in Ireland (1996-2005).](image)

Source: Health Protection Surveillance Centre
The trends outlined above reflect the trends observed in the UK where anogenital warts are the most common viral sexually transmitted infection (STI) diagnosed at genitourinary medicine (GUM) clinics, comprising 10% (81,137 of 790,443) of all diagnoses in 2005. Between 1972 and 2005, the number of all genital warts diagnoses in the UK increased by 5 and 8 fold in men and women, respectively. The burden of disease was greatest among young adults with rates among males aged 20-24 to be the highest (774/100,000) and among females those aged 16-19 years had the highest rates (730/100,000). In fact, 30% of diagnoses among females were seen in those under 20 years of age. This compares to only 11% among males in this age group.

High rates were found to be uniformly distributed across England, Wales and Northern Ireland. Rates were highest among men and women in London; 188/100,000 and 150/100,000 respectively. Elsewhere, rates in females ranged from 143/100,000 in the North West to 100/100,000 in the West Midlands. There was regional variation among male rates, from 114/100,000 in the West Midlands to 173/100,000 in the North West region.
Cervical Cancer
Persistent infection with HPV results in intraepithelial neoplasia and cancer. Recent trends in the number of cases of Cervical Intraepithelial Neoplasia III (CINIII), Squamous Cell Carcinoma and Adenocarcinoma is illustrated below (Figure 17).

Figure 17 C53.9 Morphology trends of Squamous Cell Carcinoma, Adenocarcinoma, CINIII and other cases of cervical cancer 1994-2001

While the number of incident cases of CIN III almost doubled between 1999 and 2001, the incidence of carcinoma has remained unchanged. This may be due in part to cervical screening. The incident rate is illustrated in Figure 18.
On average, 72 women die as a result of cervical cancer each year in Ireland. The mean age of these women is 56 years mean at time of death. The mean age at the time of diagnosis is 44 years.

Source: Irish Cancer Registry
Screening for cervical cancer
Despite a number of recommendations and report findings extending over two decades, a national population based cervical screening programme does not exist in Ireland (Figure 20).

Figure 20 Key reports and initiatives that influenced the establishment and development of a population based cervical screening programme in Ireland.

- 2003: National Health Strategy says phase one of cervical screening programme is being implemented in the Mid-Western Health Board and will be extended to all areas.

A pilot programme was established in October 2000 following the 1996 Report of the Department of Health Cervical Screening Committee. The Programme (phase I of the National Irish Cervical Screening Programme) is confined to women aged 25-60 years in the HSE Mid West. Women are offered a screening test every five years. Approximately 22,000 tests are performed each year. Table 7 outlines uptake by age group between 2000 and 2003.

Table 7: Annual number of smears taken by woman's age group

<table>
<thead>
<tr>
<th>Age Group</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>221</td>
<td>1,181</td>
<td>1,338</td>
<td>1,371</td>
<td>4,111</td>
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<tr>
<td>25-29</td>
<td>289</td>
<td>2,155</td>
<td>2,779</td>
<td>3,091</td>
<td>8,314</td>
</tr>
<tr>
<td>30-34</td>
<td>278</td>
<td>2,108</td>
<td>2,918</td>
<td>3,609</td>
<td>8,913</td>
</tr>
<tr>
<td>35-39</td>
<td>265</td>
<td>2,096</td>
<td>2,849</td>
<td>3,395</td>
<td>8,605</td>
</tr>
<tr>
<td>40-44</td>
<td>251</td>
<td>1,837</td>
<td>2,492</td>
<td>3,124</td>
<td>7,704</td>
</tr>
<tr>
<td>45-49</td>
<td>245</td>
<td>1,503</td>
<td>2,047</td>
<td>2,670</td>
<td>6,465</td>
</tr>
<tr>
<td>50-54</td>
<td>184</td>
<td>1,210</td>
<td>1,647</td>
<td>2,151</td>
<td>5,192</td>
</tr>
<tr>
<td>55-59</td>
<td>118</td>
<td>758</td>
<td>2,001</td>
<td>2,286</td>
<td>5,163</td>
</tr>
<tr>
<td>60 only</td>
<td>14</td>
<td>86</td>
<td>359</td>
<td>326</td>
<td>785</td>
</tr>
<tr>
<td>61+</td>
<td>41</td>
<td>316</td>
<td>631</td>
<td>678</td>
<td>1,666</td>
</tr>
<tr>
<td>Total</td>
<td>1,906</td>
<td>13,250</td>
<td>19,061</td>
<td>22,701</td>
<td>56,918</td>
</tr>
</tbody>
</table>

Source: NCSP Statistical Report

Data up to 2003 suggest that coverage was 70.1% (33,909/48,388) and was highest in the 25-34 and 55-59 age grouping (Figure 21). The latter group has been targeted more frequently with invitation letters to attend for screening before reaching the age of 61 years. The estimated uptake over a five year rolling programme is approximately 61%.
The target for a national programme, based on 2002 census figures is approximately 300,000 tests per year. Currently, 22,000 tests are performed each year as part of the regional programme. This figure is likely to be an underestimate; data relating to smears taken during opportunistic screening may not be entered onto the database. All women that participate in the ICSP Programme provide a signed form of consent. It would be unethical to include data relating to women without their prior knowledge and consent.
Implementing a HPV vaccine strategy in Ireland

Earlier, we identified 19 questions (p6) that should be addressed in the course of establishing a national vaccination campaign for the prevention of Human Papillomavirus. In light of the evidence outlined above, these questions can now be addressed below.

1. What is the burden of disease related to HPV in Ireland, or a country of similar demographic circumstances in the same region

The burden of HPV is reflected in the incidence of ano-genital warts, abnormal cervical cytology, and mortality from cervical carcinoma.

Ano-genital warts
Data suggest that the number of notifications of ano-genital warts increased significantly in recent years (p34). Table 8 outlines the trend observed in Ireland with those of our near neighbours in the UK.

<table>
<thead>
<tr>
<th>Country</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ireland</td>
<td>101.9</td>
<td>100.4</td>
<td>101.6</td>
<td>106.6</td>
<td>88.2</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>126.1</td>
<td>128.3</td>
<td>127.8</td>
<td>122.8</td>
<td>133.7</td>
</tr>
<tr>
<td>Scotland</td>
<td>109.9</td>
<td>110.8</td>
<td>114.6</td>
<td>123.4</td>
<td>126.6</td>
</tr>
<tr>
<td>Wales</td>
<td>114.7</td>
<td>112.0</td>
<td>114.0</td>
<td>117.5</td>
<td>121.9</td>
</tr>
<tr>
<td>England</td>
<td>126.2</td>
<td>128.8</td>
<td>130.7</td>
<td>136.2</td>
<td>136.4</td>
</tr>
<tr>
<td>UK</td>
<td>124.3</td>
<td>126.4</td>
<td>128.5</td>
<td>133.8</td>
<td>134.8</td>
</tr>
</tbody>
</table>

Pre-cancer and HPV 16 and HPV18
HPV 16 and HPV18 are considered to be carcinogenic to humans\(^{94}\). Cross sectional studies undertaken in the UK have demonstrated that HPV 16 and 18 are prevalent in samples taken for routine cervical screening. Samples taken from 24,510 women aged 20-64 were analysed\(^{95}\). The prevalence of HPV was found to decrease sharply with age; from 40% at age 20-24 years to 12% at 35-39 years and 7% or less above the age of 50 years. Prevalence increased with cytological grade from 10% of samples with normal cytology, 31% of borderline, to 70% mild, 86% moderate and 96% of severe dyskaryosis or worse. HPV 16 or 18 accounted for 64% of infections in women with severe or worse cytology and one or both were found in 61% of women with severe dyskaryosis but in only 2.2% of those with normal cytology. The data are presented below, Figure 22
Figure 22 Prevalence of HPV 16, HPV 18 and other high risk (HR) HPV types by histology

Source: Kitchener et al.95

*SCC: Squamous Cell Carcinoma, CGIN: cervical glandular intraepithelial neoplasia, ADCC: adenocarcinoma

Studies undertaken in Irish women also identified a high prevalence of HPV 16 and HPV 18. The findings of these studies are outlined below in Table 9 and Table 10.

Table 9 Prevalence of High Risk HPV identified in cervical screening samples undertaken in Irish women

<table>
<thead>
<tr>
<th>Author</th>
<th>HPV DNA Source</th>
<th>PCR primers used to identify all HPV +</th>
<th>No of cases</th>
<th>CINII/ CINIII/ CIS/HSIL</th>
<th>HPV – specific prevalence (%of all cases tested)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butler96</td>
<td>Fixed biopsies</td>
<td>TS-PCR</td>
<td>27</td>
<td>0/27/0/0</td>
<td>85.2 70.4 3.7 3.7 3.7 0.0 0.0</td>
</tr>
<tr>
<td>O’Leary97</td>
<td>Fixed biopsies</td>
<td>GP5/6</td>
<td>20</td>
<td>0/20/0/0</td>
<td>95.0 95.0 0.0 0.0 0.0</td>
</tr>
</tbody>
</table>

Table 10 Prevalence of High Risk HPV identified in cervical screening samples undertaken in Irish women

<table>
<thead>
<tr>
<th>Author</th>
<th>HPV DNA Source</th>
<th>PCR primers used to identify all HPV +</th>
<th>No of cases</th>
<th>SCC/ ADC</th>
<th>HPV – specific prevalence (%of all cases tested)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Leary98</td>
<td>Fixed biopsies</td>
<td>GP5/6, GP1/2</td>
<td>20</td>
<td>0/20/0/0</td>
<td>90.0 80.0 10.0 0.0 0.0</td>
</tr>
<tr>
<td>Skeyldberg99</td>
<td>Fixed biopsies</td>
<td>GP5+/6+</td>
<td>38</td>
<td>0/38</td>
<td>60.5 23.7 26.3 0.0 0.0</td>
</tr>
</tbody>
</table>

Although the studies undertaken suggest a high prevalence of High Risk types, the samples studied are small in number (n=20-38).
A recent study undertaken by Murphy et al. related to the study of 22 normal cytology samples in addition to 5 samples of cervical glandular intraepithelial neoplasia (cGIN), 38 CINI, 33CINII and 46 CINIII. Also studied were eight samples of invasive squamous (SCC) and two adenocarcinomas. A total of 12 normal ThinPrep smears, 1 cGIN, and 20 exhibiting mild, moderate and severe dyskaryosis were examined. In total 187 samples were tested. The data from this study is illustrated below, Figure 23.

Figure 23 Prevalence of High Risk HPV types in cervical biopsies and ThinPrep smear in a study of Irish women

Figure 23 may be contrasted with Figure 22, however, it is important to note that there are significant methodological differences and as such it would be unwise to compare the findings directly.

* SCC: Squamous Cell Carcinoma, CGIN: cervical glandular intraepithelial neoplasia, ADCC: adenocarcinoma

Source: Murphy et al
Cervical cancer
On average, 72 women die as a result of cervical cancer each year in Ireland. The mean age of these women is 56 years mean at time of death. The mean age at the time of diagnosis is 44 years. Incident, mortality and prevalence data for European WHO areas are presented below in Table 11. Data relating to Ireland is highlighted.

Table 11 Incidence, Mortality and Prevalence of cervical carcinoma by country and WHO region

<table>
<thead>
<tr>
<th>Country/ WHO Region</th>
<th>Incidence</th>
<th>Mortality</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Crude Rate</td>
<td>ASR (W)*</td>
</tr>
<tr>
<td>Austria</td>
<td>610</td>
<td>14.8</td>
<td>10.9</td>
</tr>
<tr>
<td>Belgium</td>
<td>667</td>
<td>12.8</td>
<td>9.4</td>
</tr>
<tr>
<td>France</td>
<td>4149</td>
<td>13.6</td>
<td>9.8</td>
</tr>
<tr>
<td>Germany</td>
<td>6133</td>
<td>14.7</td>
<td>10.8</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>24</td>
<td>10.6</td>
<td>8.7</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>753</td>
<td>9.4</td>
<td>7.3</td>
</tr>
<tr>
<td>Switzerland</td>
<td>389</td>
<td>10.8</td>
<td>8.3</td>
</tr>
<tr>
<td>Western Europe</td>
<td>12744</td>
<td>13.6</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Country/ WHO Region</th>
<th>Incidence</th>
<th>Mortality</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>389</td>
<td>25.1</td>
<td>25.2</td>
</tr>
<tr>
<td>Bosnia</td>
<td>545</td>
<td>26.6</td>
<td>21.3</td>
</tr>
<tr>
<td>Croatia</td>
<td>431</td>
<td>18</td>
<td>13.3</td>
</tr>
<tr>
<td>Greece</td>
<td>578</td>
<td>10.7</td>
<td>7.7</td>
</tr>
<tr>
<td>Italy</td>
<td>3418</td>
<td>11.6</td>
<td>8.1</td>
</tr>
<tr>
<td>Macedonia</td>
<td>167</td>
<td>16.3</td>
<td>13.9</td>
</tr>
<tr>
<td>Malta</td>
<td>14</td>
<td>7.1</td>
<td>4.8</td>
</tr>
<tr>
<td>Portugal</td>
<td>956</td>
<td>18.4</td>
<td>13.5</td>
</tr>
<tr>
<td>Serbia</td>
<td>1816</td>
<td>34.4</td>
<td>27.4</td>
</tr>
<tr>
<td>Slovenia</td>
<td>207</td>
<td>20.3</td>
<td>16.1</td>
</tr>
<tr>
<td>Spain</td>
<td>2103</td>
<td>10.3</td>
<td>7.6</td>
</tr>
<tr>
<td>Southern Europe</td>
<td>10641</td>
<td>14.4</td>
<td>10.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Country/ WHO Region</th>
<th>Incidence</th>
<th>Mortality</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td>439</td>
<td>16.3</td>
<td>12.6</td>
</tr>
<tr>
<td>Estonia</td>
<td>156</td>
<td>21.5</td>
<td>15.5</td>
</tr>
<tr>
<td>Finland</td>
<td>164</td>
<td>6.2</td>
<td>4.3</td>
</tr>
<tr>
<td>Israel</td>
<td>13</td>
<td>9.2</td>
<td>8.3</td>
</tr>
<tr>
<td>Ireland</td>
<td>164</td>
<td>8.4</td>
<td>7.2</td>
</tr>
<tr>
<td>Latvia</td>
<td>291</td>
<td>22.6</td>
<td>12.9</td>
</tr>
<tr>
<td>Lithuania</td>
<td>446</td>
<td>23.0</td>
<td>17.6</td>
</tr>
<tr>
<td>Norway</td>
<td>291</td>
<td>12.8</td>
<td>10.4</td>
</tr>
<tr>
<td>Sweden</td>
<td>485</td>
<td>10.9</td>
<td>8.2</td>
</tr>
<tr>
<td>UK</td>
<td>3181</td>
<td>10.5</td>
<td>8.3</td>
</tr>
<tr>
<td>Northern Europe</td>
<td>5647</td>
<td>11.7</td>
<td>9</td>
</tr>
</tbody>
</table>

Source: GLOBOCAN 2002, IARC^102

*Crude and Age-Standardised (World) rates, per 100,000
The data suggest that Ireland compares favourably with other countries in the WHO-Europe region (Figure 24 and Figure 25).

Figure 24 Age-Standardised Incidence of cervical carcinoma in WHO Northern Europe

Figure 25 Age-Standardised mortality from cervical carcinoma in WHO Northern Europe

Source: GLOBOCAN 2002, IARC
2. **What is the population attitude towards cervical cancer and HPV**

During November 2006, funding was secured from the Health Research Board (HRB) to a CERVIVA, a cervical cancer research consortium was launched. The consortium identified the attitudes of women to cervical screening and HPV oncogenic testing as one of eight research objectives. The consortium is being led by Prof. John O’Leary, Trinity College, Dublin.

3. **What is the peak age of infection with HPV, and what are the implications for the choice of target age group?**

The incidence of anogenital warts appears to peak among those aged 20-29 years (Figure 26). However, it is important to note these figures may be influenced by the manner in which surveillance data is collected and collated.

*Figure 26 Number of notifications for ano-genital warts by age in Ireland during 2005*

Data from Kitchener et al.\(^9\) (Figure 27) outlines the prevalence of High Risk types by age
4. What is the number of doses needed to generate adequate immunity through high risk periods, and in particular, is it possible to use a two-dose vaccination schedule instead of a three-dose schedule?

The vaccine products that are currently licensed recommend a three dose schedule (0, 2 and 6 months).

5. Might HPV vaccination be integrated into the infant immunisation schedule or at school entry, at any time in the future, with or without a booster dose just before the high-risk period?

The vaccine products that are currently licensed recommend a three dose schedule for young women aged 9 to 26 years.

In order to give an estimate of the numbers of children (male and female) that this is likely to affect, statistics relating to the educational year 2002/2003 are outlined below in Table 12. The data suggest that the educational system captures 100% of children between the ages of 6 and 13 years.
<table>
<thead>
<tr>
<th>Age (on 1st January 2003)</th>
<th>3-5</th>
<th>6-11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
<th>&gt;21*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Level</td>
<td>83,468</td>
<td>324,499</td>
<td>34,598</td>
<td>3,024</td>
<td>1,039</td>
<td>662</td>
<td>625</td>
<td>531</td>
<td>245</td>
<td>37</td>
<td>13</td>
<td>13</td>
<td>448,754</td>
</tr>
<tr>
<td>Second Level</td>
<td>-</td>
<td>68</td>
<td>22,154</td>
<td>53,672</td>
<td>56,906</td>
<td>58,512</td>
<td>57,415</td>
<td>47,581</td>
<td>22,609</td>
<td>7,108</td>
<td>3,667</td>
<td>13,904</td>
<td>343,596</td>
</tr>
<tr>
<td>Third Level</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7</td>
<td>3,148</td>
<td>17,075</td>
<td>25,880</td>
<td>26,049</td>
<td>65,164</td>
<td>137,323</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>83,468</td>
<td>324,567</td>
<td>56,752</td>
<td>56,696</td>
<td>57,945</td>
<td>59,174</td>
<td>58,047</td>
<td>51,260</td>
<td>39,929</td>
<td>33,025</td>
<td>29,729</td>
<td>79,081</td>
<td>929,673</td>
</tr>
<tr>
<td>Census 2002</td>
<td>165,967</td>
<td>322,475</td>
<td>56,627</td>
<td>56,677</td>
<td>59,474</td>
<td>60,882</td>
<td>61,682</td>
<td>63,039</td>
<td>63,009</td>
<td>64,576</td>
<td>66,355</td>
<td>385,177</td>
<td>1,425,940</td>
</tr>
<tr>
<td>Proportion of all children in education (%)</td>
<td>50.3</td>
<td>100.6</td>
<td>100.2</td>
<td>100.0</td>
<td>97.4</td>
<td>97.2</td>
<td>94.1</td>
<td>81.3</td>
<td>63.4</td>
<td>51.1</td>
<td>44.8</td>
<td>20.5</td>
<td>65.2</td>
</tr>
</tbody>
</table>

* for those aged 21 years and over, to estimate the proportion of the population in education, it is assumed that the denominator is based on the number aged between 21 and 26 years of age. This is a crude measure since those individuals in education aged 21 years and over will range from 21 to 85+ years.
6. Can the vaccine be administered simultaneously with other vaccines such as those containing measles and rubella vaccines and tetanus toxoid?

The vaccine can be administered at the same time as other vaccines, generally in another area of the body.

7. What are the cold chain requirements for the vaccine?

Vaccine manufacturers recommend that the vaccine should be stored refrigerated at 2 to 8°C and must be protected from sunlight.

8. What is the cost of the vaccine, and what are the potential mechanisms to finance this?

The cost of the vaccine in Ireland is currently quoted at €200 per dose. This cost does not take account of indirect costs associated with the acquisition, storage and administration of the vaccine.

9. What proportion of cervical cancer and other HPV related disease in a region or country are attributable to the HPV types targeted by the available vaccines?

Data from Irish studies suggest that High Risk HPV 16 and HPV 18 are associated with more than 60% of all cases of cervical cancer. International studies suggest that the fraction of squamous cell carcinomas or adenocarcinomas attributable to HPV16 or HPV 18 was 70% and 86% respectively.

Other cancer

Parkin et al outline the cancers and numbers affected by cancers attributable to High Risk HPV (Table 13). The data contrast differences between developed and developing worlds. The data also illustrate the range of cancers that are related to HPV.

<table>
<thead>
<tr>
<th>Site</th>
<th>Developed countries</th>
<th>% all cancers</th>
<th>Attributable cancers %</th>
<th>Total cancers</th>
<th>% all cancers</th>
<th>Attributable cancers %</th>
<th>Total cancers</th>
<th>% all cancers</th>
<th>Attributable cancers %</th>
<th>World</th>
<th>% all cancers</th>
<th>Attributable cancers %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>83,400</td>
<td>100</td>
<td>83,400</td>
<td>1.7</td>
<td>409,400</td>
<td>100</td>
<td>409,400</td>
<td>7.0</td>
<td>492,800</td>
<td>100</td>
<td>492,800</td>
<td>4.5</td>
</tr>
<tr>
<td>Penis</td>
<td>5,200</td>
<td>40</td>
<td>2,100</td>
<td>0.04</td>
<td>21,100</td>
<td>40</td>
<td>8,400</td>
<td>0.14</td>
<td>26,300</td>
<td>40</td>
<td>10,500</td>
<td>0.1</td>
</tr>
<tr>
<td>Vulva, vagina</td>
<td>18,300</td>
<td>40</td>
<td>7,300</td>
<td>0.2</td>
<td>21,700</td>
<td>40</td>
<td>8,700</td>
<td>0.2</td>
<td>40,000</td>
<td>40</td>
<td>16,000</td>
<td>0.2</td>
</tr>
<tr>
<td>Anus</td>
<td>14,500</td>
<td>90</td>
<td>13,100</td>
<td>0.3</td>
<td>15,900</td>
<td>90</td>
<td>14,300</td>
<td>0.2</td>
<td>30,400</td>
<td>90</td>
<td>27,400</td>
<td>0.2</td>
</tr>
<tr>
<td>Mouth</td>
<td>91,100</td>
<td>3</td>
<td>2,700</td>
<td>0.1</td>
<td>183,000</td>
<td>3</td>
<td>5,500</td>
<td>0.1</td>
<td>274,100</td>
<td>3</td>
<td>8,200</td>
<td>0.1</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>24,400</td>
<td>12</td>
<td>2,900</td>
<td>0.1</td>
<td>27,700</td>
<td>12</td>
<td>3,300</td>
<td>0.1</td>
<td>52,100</td>
<td>12</td>
<td>6,300</td>
<td>0.1</td>
</tr>
<tr>
<td>All sites</td>
<td>5,016,100</td>
<td>111,500</td>
<td>2.2</td>
<td>5,827,500</td>
<td>449,600</td>
<td>7.7</td>
<td>10,843,600</td>
<td>561,200</td>
<td>5.2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Parkin et al.
HPV 6/11
Have low carcinogenic potential however they are known to give rise to ano-genital warts.

10. **What fraction of cervical cancer overall will be prevented by a vaccine against HPV 16 and 18?**
To date most clinical trials have used pre-cancer end-points to monitor vaccine efficacy. Studies designed to determine vaccine effectiveness in preventing cervical cancer are on-going. Long term efficacy trials are currently under way in Finland and Scandinavia (the Nordic HPV vaccine Trials). These are double blinded, controlled, population-based phase III efficacy studies. A randomised, double-blinded, controlled, population-based efficacy trial is also taking place in Guanacaste, Costa Rica. The Nordic trials will have a high power to detect the impact of vaccination on lesions that are CINIII or greater. Results are expected by 2015-2020\(^{103}\).

It is unclear if a decline in the prevalence of High-Risk HPV will leave an ecological vacuum that will be filled by other HR HPV types, in which case the overall effectiveness of vaccination would be reduced. This will be addressed in the long term efficacy trials.

11. **Will immunity induced by vaccines alter the distribution of other non-vaccine HPV types**
Research is on-going to address this question, though some recent evidence suggests that there may be some cross-protection\(^{76}\). This question needs to be addressed in the form of national and international post-licensure studies.

12. **Will a vaccination programme against a sexually transmitted infection prove acceptable to adolescents who are not sexually active and their parents?**
The answer to this is unknown. Evidence from the UK suggest that safety and effectiveness will determine uptake, however, the general lack of awareness of the role of HPV in cervical cancer could lead to stigmatization of the vaccine\(^{104}\). This may have a negative impact on uptake. A study undertaken to track mother's attitudes to childhood vaccination suggest that the “public” want clarity, consistency, factual information and openness from those delivering immunisation services\(^{105}\).

There is anecdotal evidence in this country, to suggest that some parents are seeking to have their children to be vaccinated while others have expressed concerns that vaccination would result in promiscuity. Such opinions have been
expressed by media sources. An important issue regarding acceptability relates to whether or not the vaccine is perceived as a vaccine against cancer or as a “sex jab”. The Irish media have largely favoured the former (Table 14).

Table 14 Newspaper coverage of HPV vaccine between June and December 2006

<table>
<thead>
<tr>
<th>Newspaper</th>
<th>Date</th>
<th>Headline</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Star</td>
<td>6th September</td>
<td>Cancer Vaccine on the way. Wonder drug saves lives</td>
</tr>
<tr>
<td>Daily Mail</td>
<td></td>
<td>Calls for immunisation programme as Ireland gears up for cervical jabs – Outrage over €300 cost of cancer vaccine</td>
</tr>
<tr>
<td>The Sun</td>
<td></td>
<td>Irish women get €300 vaccine – Cervical jab to save kids from cancer</td>
</tr>
<tr>
<td>Mirror</td>
<td></td>
<td>Cancer vaccine not here until 2008 – Government accused of disease fight delay</td>
</tr>
<tr>
<td>Irish Examiner</td>
<td></td>
<td>Cervical cancer vaccine raises hopes</td>
</tr>
<tr>
<td>The Irish Times</td>
<td></td>
<td>Cervical cancer vaccine to be available soon</td>
</tr>
<tr>
<td>Irish Independent</td>
<td></td>
<td>New jab will help protect against cervical cancers – but women still need regular tests</td>
</tr>
<tr>
<td>Sunday Tribune</td>
<td>9th October</td>
<td>Cancer jab should not mean green light for underage sex, says doctor</td>
</tr>
<tr>
<td>Daily Mail</td>
<td></td>
<td>“I don’t enjoy having smear tests. But it’s one of those things you’ve just got to do”</td>
</tr>
<tr>
<td>Daily Mail</td>
<td>2nd November</td>
<td>Men could receive jab against sex virus to cut cancer rates</td>
</tr>
</tbody>
</table>

Other issues to consider in an Irish context are those that influence both the choice of target population and issues of acceptability are attitudes of Irish people towards sex and age at first vaginal sex. In this respect a number of studies have been undertaken in recent years.

Findings from the Irish Study of Sexual Health and Relationships suggested that the median age at which women became sexually active was between 17 and 23 years. Of those aged between 18 and 24 years at the time of the survey, 10-20% reported sexual activity by the age of 16 years.

Figure 28 Proportions having sex before age 17: by gender

Source: ISSHR
These findings echo those from older surveys such as SLÁN (Survey of Lifestyle, Attitudes and Nutrition) and CLAN (College Lifestyle and Attitudinal National Survey). Both SLÁN surveys from 1998 and 2002 consistently show that a high proportion of those aged under the age of 20 years are sexually active (Table 15 and Table 16).

Table 15 Percentage sexual activity by age (SLÁN 98 and SLÁN 02)

<table>
<thead>
<tr>
<th>Age</th>
<th>SLÁN 98 (n=4007)</th>
<th>SLÁN 02 (n=3565)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>53.5</td>
<td>50.0</td>
</tr>
<tr>
<td>20-24</td>
<td>72.4</td>
<td>77.9</td>
</tr>
<tr>
<td>25-29</td>
<td>85.8</td>
<td>85.8</td>
</tr>
<tr>
<td>30-34</td>
<td>88.7</td>
<td>89.1</td>
</tr>
<tr>
<td>35-39</td>
<td>91.8</td>
<td>90.2</td>
</tr>
<tr>
<td>40-44</td>
<td>85.7</td>
<td>84.2</td>
</tr>
<tr>
<td>45-50</td>
<td>80.8</td>
<td>79.7</td>
</tr>
<tr>
<td>All</td>
<td>82.6 (*82.0)</td>
<td>84.3 (*82.1)</td>
</tr>
</tbody>
</table>

* Age adjusted to the 2002 Census

Source: Shiely et al

Table 16 Age of sexual onset and number of sexual partners in lifetime by gender

<table>
<thead>
<tr>
<th>Age at first sexual intercourse</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 14 years</td>
<td>3.4</td>
<td>1.8</td>
<td>2.4</td>
</tr>
<tr>
<td>15-16 years</td>
<td>26.8</td>
<td>21.9</td>
<td>23.8</td>
</tr>
<tr>
<td>17 years or older</td>
<td>69.8</td>
<td>76.3</td>
<td>73.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of sexual partners</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 people</td>
<td>58.0</td>
<td>71.3</td>
<td>66.1</td>
</tr>
<tr>
<td>4-5 people</td>
<td>14.6</td>
<td>13.7</td>
<td>14.1</td>
</tr>
<tr>
<td>6 or more people</td>
<td>27.4</td>
<td>15.0</td>
<td>19.9</td>
</tr>
</tbody>
</table>

Source: CLAN Survey
The CLAN survey suggests that as many as 25% of young (educated) adolescents are sexually active by the age of 16 years. These findings are consistent with those from a survey of attitudes and behaviour carried out in a Third Level Institution in Dublin (Figure 30).

**Figure 30 Age of first sexual experience among students attending an Irish Third Level Institution**

![Age of First Sex](source)

Larger scale studies undertaken in the UK suggest that 20.4% of women experienced vaginal intercourse before the age of 16.

**Table 17 Sexual behaviour in Britain**

<table>
<thead>
<tr>
<th>Age (years) at time of interview</th>
<th>16-19</th>
<th>20-24</th>
<th>25-29</th>
<th>30-34</th>
<th>35-39</th>
<th>40-44</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Age (yrs) at first intercourse (10th, 90th centiles)</td>
<td>16 (14-19)</td>
<td>17 (14-20)</td>
<td>17 (14-21)</td>
<td>17 (14-21)</td>
<td>17 (14-22)</td>
<td>17 (14-23)</td>
<td>17 (14-21)</td>
</tr>
<tr>
<td>Aged under 16 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29.9% (25.7-34.5)</td>
<td>25.8% (22.0-30.1)</td>
<td>29.2% (25.7-32.9)</td>
<td>29.5% (26.5-32.7)</td>
<td>23.6% (20.7-26.7)</td>
<td>27.1% (23.8-30.8)</td>
<td>27.4% (26.0-28.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Age (yrs) at first intercourse (10th, 90th centiles)</td>
<td>16 (14-19)</td>
<td>16 (14-20)</td>
<td>17 (15-20)</td>
<td>17 (15-21)</td>
<td>17 (15-21)</td>
<td>17 (15-22)</td>
<td>17 (15-21)</td>
</tr>
<tr>
<td>Aged under 16 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25.6% (22.0-29.5)</td>
<td>28.4% (25.1-32.1)</td>
<td>24.5% (21.8-27.5)</td>
<td>16.7% (14.6-19.0)</td>
<td>17.0% (14.8-19.3)</td>
<td>13.8% (11.6-16.4)</td>
<td>20.4% (19.3-21.5)</td>
<td></td>
</tr>
</tbody>
</table>

**Source: Wellings et al**

Therefore survey data from Ireland and the UK suggest that a significant proportion of young men and women are sexually active before the age of 16. This implies that the target population for vaccination is below age of 16 years, precisely how young is unclear. This raises ethical issues that will determine the acceptability of the vaccine among the population.
13. **Should teenage boys be vaccinated as well as teenage girls?**
If the HPV vaccines are proven to be efficacious in males, there is likely to be considerable interest in vaccinating young adolescent males with the quadrivalent vaccine in order to reduce their risk for anogenital warts. Although the burden of disease associated with HPV 16 and HPV 18 is considerably less in men than women, when compared to other conditions for which we commonly vaccinate, the number of cases of HPV 16 and HPV 18 associated penile and oropharyngeal cancers in males is not insignificant.

14. **Will booster vaccinations be necessary, and if so when?**
The durability of the immune response to vaccination is unknown.

15. **How will a vaccination programme affect current programmes for cervical cancer screening, and when should screening change in response?**
Ireland does not have a population based cervical cancer screening programme, the current pilot is due for national role out, no timescales have yet been established. Further modelling and research is required to determine the best use of HPV testing and how this can be used to improve sensitivity and specificity of current screening tests. It is likely that such testing will lead to more targeted screening of women which in turn will affect the frequency of testing.

16. **What benefits might vaccination confer on adults who are already infected with HPV?**
There is no evidence to suggest that this is effective at this time.

17. **Should older sexually active adults be included as part of a catch-up campaign at the outset of a vaccination programme?**
There is no evidence to suggest that this is effective at this time.

18. **Should any catch-up campaign be aimed at specific subgroups of the population?**
The American Advisory Committee on Immunisation Practices (ACIP) issued provisional recommendations for the use of quadrivalent HPV vaccine and suggested routine vaccination with three doses of vaccine for females 11-12 years of age with the option of starting in females as young as 9 years of age. Catch-up vaccination is recommended for females 13-26 years of age not previously vaccinated.
19. **What will be the cost effectiveness of various strategies for vaccination programmes?**
There is no evidence available for an Irish context.
Conclusions

Human Papillomavirus is a sexually transmitted viral infection. The infection affects both men and women. Annual rates of incident infection in young women are approximately 5-15% and infections by high-risk types, particularly HPV 16 are the most frequent. Overall HPV positivity in cytologically normal women has been reported at levels between 1.5-39%. The incidence and prevalence of HPV infections peak in young adults in most study populations. Prevalence is higher in populations of commercial sex workers and men with human immunodeficiency virus. There is a paucity of studies on the natural history of HPV infection in men and on HPV infection at non-genital sites.

Viral DNA persists for a median of approximately 1 year, with high-risk types persisting somewhat longer than low-risk types.

Evidence for the carcinogenic potential of HPV is derived from three lines of epidemiological data that include results from HPV type-specific case-control studies as well as prospective cohort studies and case series from five continents. Traditionally, prospective cohort studies are considered to provide the highest level of evidence, however, in the case of HPV, there are limitations because of the small number of cancer end-points and the need to focus on the surrogate end-point of CINIII. As a result, in this instance, data from case-control studies carry more weight as they relate to the evaluation of a larger number of invasive cancers. Virtually all cervical cancers were found to contain HPV DNA. The large and comprehensive case series permitted consideration of the relative frequency of different HPV types across cervical lesions of increasing severity. The classification of risk derived from epidemiological evidence relates to phylogenetic classification.

Vaccine studies suggest a high level of safety and efficacy that is likely to remain beyond 5 years in protecting against high-risk HPV infection and their associated pre-cancerous lesions. However, many gaps in knowledge remain.

Surveillance data from Ireland suggests that the HPV burden is increasing among young adults. The incidence of cervical cancer has remained relatively stable over the last decade despite a rise in the incidence of cervical intraepithelial neoplasia. Young adults who are sexually active and exposed to high-risk HPV will not benefit from HPV vaccination. Effective screening and treatment programmes are very important for these individuals. The following tables taken from Franco et al outline the gaps in knowledge and priorities for research on prophylactic vaccines (Table 18) and the integration of HPV vaccines into cervical cancer screening (Table 19).
### Table 18 Essential findings, gaps in knowledge, and priorities for research on prophylactic HPV vaccines

<table>
<thead>
<tr>
<th>Research areas</th>
<th>Findings that are essential to assist prevention efforts</th>
<th>Gaps in knowledge and research priorities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanisms of protection</td>
<td>Virus-like particle (VLP) vaccines induce a strong immune response, including high-titer neutralizing antibodies, that is protective against persistent HPV infection and cervical precancerous lesions</td>
<td>Determine the extent of cross-type neutralization induced by VLPs in in-vitro assays; establish an immune correlate of protection; determine if post-vaccination exposure to HPV under normal conditions boosts immune responses; determine if type replacement occurs in populations with high vaccine coverage; determine if herd immunity is induced</td>
</tr>
<tr>
<td>Clinical trials and demonstration projects</td>
<td>By mid-2006 phase II trials have been completed and phase III trials have begun to confirm that strong type-specific protection against persistent HPV infection and cervical dysplasia is achieved with both candidate vaccines</td>
<td>Determine duration of protection; determine degree and duration of cross-protection against types not included in the vaccine; determine safety and efficacy of the vaccines in HIV and other immunocompromised individuals according to degree and changes in immune function; determine efficacy in males and in blocking sexual transmission; determine the impact of vaccination on prevalent infections; determine vaccine efficacy against other anogenital and oral infections and lesions</td>
</tr>
<tr>
<td>Vaccine delivery</td>
<td>Vaccination is among the most cost-effective public health measures for disease prevention; maximum impact of vaccination expected in developing countries with high cervical cancer rates; worldwide experience with hepatitis B vaccination serves as useful model to anticipate problems in delivery; key importance of World Health Organization and donor institutions to ensure consistency in distribution and acceptability</td>
<td>Surveys to determine disease burden, HPV type prevalence, and vaccine acceptability in key understudied areas; health promotion research to improve vaccine acceptability in culturally diverse settings; demonstration projects in select countries may be useful to stimulate acceptance and demand for the vaccine; development of “investment cases” needed to highlight the potential benefits of HPV vaccination in specific settings; generation of intellectual property &quot;maps&quot; would help provide freedom to operate information for potential regional producers</td>
</tr>
<tr>
<td>Next generation of vaccines</td>
<td>Preclinical studies suggest that candidates might address limitations, such as high production costs, need for cold chain, requirement for three intramuscular injections, type-restricted efficacy, and lack of therapeutic activity</td>
<td>Will the experience with safety and efficacy of first generation of vaccines reveal correlates of protection to simplify clinical development of newer vaccines? Is commercialization realistic given the intellectual property constraints? Develop communication strategies to prevent health authorities in some countries to delay implementation of existing vaccines under the assumption that a second generation of vaccines is on the way</td>
</tr>
</tbody>
</table>

### Table 19 Essential findings, gaps in knowledge, and priorities for research on the integration of HPV vaccination into cervical cancer screening

<table>
<thead>
<tr>
<th>Research areas</th>
<th>Findings that are essential to assist prevention efforts</th>
<th>Gaps in knowledge and research priorities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost effectiveness of interventions</td>
<td>Balance of marginal benefits for combining HPV vaccination to screening; current inequity: cost-effective interventions are available but unused in developing countries, whereas expensive interventions often used in developed countries for marginal gains; wider international problem of lack of equity in healthcare in developing countries</td>
<td>What are the cost implications for screening being met from a different source than those covering costs for HPV vaccines? How will a vaccine against HPV compete for resources with other vaccines aimed mainly at preventing childhood disease and mortality? Operational research on the design and acceptability of services; research on how to increase coverage of screening; demonstration projects to show that disease incidence will not increase from less aggressive screening and treatment with new technologies; research on screening follow-up algorithms.</td>
</tr>
<tr>
<td>Impact of vaccination on screening</td>
<td>Screening will have to continue because of lack of vaccine coverage for all oncogenic HPV types, presumed lack of therapeutic efficacy, and to monitor loss of protection; decrease in prevalence of cervical precancerous lesions will lower the positive predictive value of cytology; potential situation to avoid: favoring vaccine uptake among women who are more likely to be screened while not doing enough to promote vaccination among those who fail to comply with screening</td>
<td>Will the performance characteristics of cytology suffer in conditions of low lesion prevalence? Can liquid-based cytology and automated technologies help prevent the possible loss of sensitivity and specificity of cytology? Can HPV testing followed by cytologic triage serve as a more rational approach to screen vaccinated women? Can age of screening onset be raised in vaccinated women? Can infection and cytology registries serve as a surveillance tool to monitor the effectiveness of vaccination? Health promotion studies of barriers to vaccine uptake and screening</td>
</tr>
</tbody>
</table>
With regard to implementation of an immunisation programme suitable to meet the needs of the population; Franco et al summarise the Public Health knowledge gaps and Public Health priorities (Table 20). Although the gaps identified relate to the global knowledge deficit, such deficits need to be taken into account when considering local immunisation policy.

Table 20 Essential findings, gaps in knowledge, and priorities for public health policy concerning implementation of HPV vaccines into immunisation programmes

<table>
<thead>
<tr>
<th>Public health areas</th>
<th>Findings that are essential to assist prevention efforts</th>
<th>Gaps in knowledge and public health priorities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decision making</td>
<td>World Health Organization (WHO) establishes licensing criteria based on best available scientific evidence for advising member countries; key criteria: vaccine efficacy from phase III trials, disease burden and cost-effectiveness</td>
<td>Proper quantification of cervical cancer burden, cost-effectiveness, and sustainability of vaccination in light of existing cervical cancer control programmes must be country and setting specific; need to establish population-based tumor registries in sentinel areas to monitor post-vaccination effects</td>
</tr>
<tr>
<td>Safety, quality and efficacy of vaccines</td>
<td>Meeting vaccine performance standards is the responsibility of manufacturers; adopt guidelines proposed by WHO for National Regulatory Authorities (NRA)</td>
<td>Should individual countries that can afford the costs of independent monitoring establish their own NRAs? International agreement on immunological correlates of protection and feasible trial endpoints</td>
</tr>
<tr>
<td>Post-market surveillance</td>
<td>Post-licensing monitoring must be done via phase IV studies</td>
<td>Need to determine efficacy and safety in conditions such as: (i) incomplete doses, (ii) simultaneous administration of other vaccines, (iii) underlying chronic and infectious diseases that may compromise immune response or affect safety, (iv) long-term follow-up, (v) suboptimal delivery; determine efficacy against other HPV-induced diseases; determine risk of diseases that could be linked to side effects of vaccination</td>
</tr>
<tr>
<td>Vaccine acceptability</td>
<td>Misunderstanding and misconceptions about transmission of HPV, its role in cervical cancer, and need for vaccination may hamper vaccine acceptability</td>
<td>Determine societal determinants of vaccine acceptability; Inform decision makers about the benefits of vaccination to prevent delayed implementation; Determine most effective means of communicating HPV-and cervical cancer-related information to healthcare providers and the population; Determine factors contributing to refusal to vaccinate</td>
</tr>
<tr>
<td>Delivery costs</td>
<td>Experience with tiered-pricing and pooled procurement used for other vaccine-preventable diseases</td>
<td>Concerted effort among WHO, GAVI, country stakeholders and vaccine suppliers to secure affordable vaccine costs for developing countries; provide incentives for developing countries to accelerate the introduction of HPV vaccines; investigate feasibility of a strategy of advanced market commitment to guarantee vaccine availability at a reasonable cost</td>
</tr>
</tbody>
</table>
Recommendations

The primary purpose of vaccination is to prevent disease and reduce the burden of illness. A successful vaccination campaign is characterised by its ability to achieve these objectives in an equitable and fair way such that the health of the population benefits as a whole.

HPV vaccination has the potential to make a significant impact on the burden of disease caused by cervical cancer. However, significant knowledge gaps remain. The challenge for decision makers will be to reach a consensus that reflects existing knowledge and is sufficiently flexible to adapt to new and emerging evidence.

1. Decisions made in relation to HPV should be consistent with existing national guidance on vaccination policies. *Immunisation Finance Policies and Practice*

2. Policies should take account of assurance matters such as the purchase and delivery of the vaccine. *Assure vaccine purchase.*

3. Access to the intervention should be equitable. Delivery should be to a high standard and subject to regular audit and evaluation to ensure that delivery is consistent with policy and that patients are being cared for appropriately *Assure service delivery.*

4. An integral part of delivery is a means to monitor trends in uptake, and measure the impact of the intervention. *Sustain and improve Coverage levels.*

5. This implies that a method of surveillance exists that is capable of measuring trends and the impact of vaccination among those targeted. This will enhance the evidence base and thereby inform policy development. *Conduct surveillance of vaccine coverage and safety.*

6. In effect, the desired goal of a successful campaign is the control and prevention of infectious disease. Given the complex natural history of HPV, it may take two decades for a national campaign to bear fruit. This emphasises the need to ensure that there are links between, vaccination programmes, screening programmes, treatment providers, outcome and registry data.

In order to assume these roles successfully, there should be a sensitivity analysis undertaken to determine the cost utility of vaccination taking account of the uncertainties identified.
### Table 21 Biological properties of each HPV genus

<table>
<thead>
<tr>
<th>Genus</th>
<th>Biological properties</th>
</tr>
</thead>
</table>
| Alpha-papillomavirus | Mucosal and cutaneous lesions in humans and primates  
High-and low-risk classification based on molecular  
biological data—high-risk types (pre-and malignant lesions)  
immortalize human keratinocytes;  
low-risk types (benign lesions) do not.  
Recent compilations of epidemiological  
data demonstrate more frequent association of specific  
species as high-risk types. |
| Beta-papillomavirus | Cutaneous lesions in humans  
Infections exist in latent form in general population,  
activated under conditions of immune suppression  
Also referred to EV-HPV types due to close association  
with disease Epidermodysplasia verruciformis (EV) |
| Gamma-papillomavirus | Cutaneous lesions in humans—histologically distinguishable by intracytoplasmic inclusion bodies  
specific for type species |
| Delta-papillomavirus | Lesions in ungulates  
Induces fibropapillomas in the respective host  
Trans-species transmission occurs inducing sarcoids |
| Epsilon-papillomavirus | Bovine papillomavirus cutaneous papillomas in cattle |
| Zeta-papillomavirus | Cutaneous lesions in horses |
| Eta-papillomavirus | Avian papillomaviruses  
Cutaneous lesions in host |
| Theta-papillomavirus | Avian papillomaviruses  
Cutaneous lesions in host |
| Iota-papillomavirus | Rodent papillomaviruses  
Cutaneous lesions |
| Kappa-papillomavirus | Isolated from rabbits  
Cutaneous and mucosal lesions |
| Lambda-papillomavirus | Animal papillomaviruses  
Benign mucosal and cutaneous lesions |
| Mu-papillomavirus | Human papillomaviruses  
Cutaneous lesions—histologically distinguishable  
by intracytoplasmic inclusion bodies specific  
for type species |
| Nu-papillomavirus | Human papillomavirus  
Benign and malignant cutaneous lesions |
| Xi-papillomavirus | Bovine papillomaviruses  
Induce true papillomas in host.  
Cutaneous or mucosal lesions |
| Omikron-papillomavirus | Isolated from genital warts in cetaceans |
| Pi-papillomavirus | Isolated from hamsters  
Mucosal lesions |
<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
<th>Type species</th>
<th>Other papillomavirus types</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-papillomavirus</td>
<td>1</td>
<td>HPV 32 (X74475)</td>
<td>HPV 42 (M73236)</td>
<td>More frequently in benign lesions (low-risk). Oral or genital mucosa. Third ORF in ELR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HPV 3 (X74462)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HPV 28 (U31783)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HPV 29 (U31784)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>HPV 78</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>HPV 94a (AJ620211)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>HPV 10 (X74465)</td>
<td></td>
<td>More frequently cause cutaneous than mucosal lesions. Low-risk. E5 biologically different</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>HPV 61 (U31793)</td>
<td>HPV 72 (X94164)</td>
<td>Mucosal lesions. Lower risk</td>
</tr>
<tr>
<td></td>
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<td>Common skin warts. Frequently in benign genital lesions in children. Several larger</td>
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<td>Deer papillomavirus (DPV) (M11910)</td>
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<td>Ovine papillomavirus 1 (OvPV1) (U83594)</td>
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<td>E5 gene in ELR with transforming properties. Trans-species infection—</td>
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<td>Bovine papillomavirus 1 (BPV 1) (X02346)</td>
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<td>Psittacus erithacus timneh papillomavirus (PePV, parrot papillomavirus) (AF420235)</td>
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Table 24 Characteristics of species within specific genera\textsuperscript{16}

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<th>Genus</th>
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<td>Iota-papillomavirus</td>
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<td>Mastomys natalensis papillomavirus (MnPv) (U01834)</td>
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<td>Kappa-papillomavirus</td>
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<td>Cottontail rabbit papillomavirus (CRPV) (K02708)</td>
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<td>High divergence within the E6 and E7 ORFs described for different isolates</td>
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<td>Rabbit oral papillomavirus (ROPV) (AF227240)</td>
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<td>Associated with cutaneous lesions</td>
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<td>Lambda-papillomavirus</td>
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<td>ELR is 1500 bp in length</td>
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<td>Felis domesticus (cat) papillomavirus (FdPV) (AF377865)</td>
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<td>ELR is 1271 bp in length</td>
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<td>Histologically distinct heterogenous intracytoplasmic inclusion bodies</td>
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<td>Several larger uncharacterized ORFs scattered throughout the genome. ELR</td>
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<td>only 17 nt. All E2 binding sites in URR modified</td>
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<td>BPV 4 (X05817) BPV 6 (AJ620208)</td>
<td>E8 gene within E6 region of BPV4 has transforming properties—similar to E5 of BPV1h</td>
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<td>E7 ORF absent. Several larger ORFs in L1 ORF region</td>
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<td>Hamster oral papillomavirus (HaOPV) (E151110)</td>
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<td>No ELR—partial overlap between E2 and L2 ORFs</td>
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References


