Introduction

Human papillomavirus (HPV) is a double stranded DNA virus that infects squamous epithelia including the skin and mucous membranes of the upper respiratory and anogenital tracts. There are more than 100 different types of HPV, most of which infect the cutaneous epithelium and are responsible for common skin warts (verrucae). Some 40 types can infect the genital tract, where infection is associated with genital warts, and multiple cancers of which cancer of the cervix is the most significant. In addition however, HPV is associated with cancers of the vulva, vagina, anus, penis, and with various oropharyngeal cancers in men and women. The types that infect the genital tract are categorized, according to their epidemiologic association with cervical cancer, into low-risk (non-oncogenic), and high-risk (oncogenic) types.

Epidemiology

Genital HPV infection is the most common sexually transmitted infection worldwide. Transmission occurs most frequently during vaginal, oral or anal sexual intercourse, but can occur following nonpenetrative sexual activity, or genital contact. Genital warts are highly contagious, with two-thirds of people who have sexual contact with an infected partner developing warts. Non-sexual routes of HPV transmission include vertical transmission from mother to newborn baby.
Chapter 10 Human papillomavirus

The clinical spectrum of HPV disease ranges from asymptomatic infection, to benign warts, to invasive cancer.

Most genital HPV infections are asymptomatic and transient, with 70% of new genital HPV infections clearing within one year, and 91% within two years. High-risk types are more likely to result in persistent infection than low-risk types. The most common clinically significant manifestation of persistent genital HPV infection is cervical intraepithelial neoplasia (CIN).

Over a number of years, low-grade CIN, or CIN1, may lead to CIN2 or CIN3. CIN. Due to the risk of these higher grades progressing to cancer, they are considered cervical cancer precursors. Persistent infection by high-risk types is detectable in more than 99% of cervical cancers.

There are 13 high risk types (i.e. HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68). In Europe, types 16 and 18 are responsible for over 70% of cervical cancers. Low-risk types 6 and 11 are associated with over 90% of genital warts.

Worldwide the prevalence of cervical HPV infection varies from 1.4% to 25.6%. The most common type is 16 followed by type 42, 58, 31, and 18. HPV 16 is twice as common as any other high-risk type worldwide except sub-Saharan Africa where HPV 35 is equally common. Of note, infection with one type of HPV does not prevent infection with other types. Of persons infected with genital HPV, between 5% and 30% are infected with multiple types of the virus.

High risk HPV types are responsible for about 90% anal cancers, 65% vaginal cancers, 60% oropharyngeal cancers, 50% vulvar cancers and 35% penile cancers. All told, HPV is responsible for 5.2% of the global cancer burden.

HPV 6 and 11 are responsible for approximately 90% of genital warts and 10% of low grade cervical intraepithelial neoplasia (CIN1).

Risk Factors
Risk factors associated with genital HPV infection include younger age at sexual initiation, number of sexual partners, and the sexual history of the partner (number of previous sexual partners). In the United States, it is estimated that approximately 1% of sexually active adults have visible genital warts and that at least 15% have subclinical infection, as determined by an HPV DNA assay. The highest rates of HPV infection occur in the 18-28 year age group, with an estimated 80% of sexually active women becoming infected with at least one type of HPV by age 50 years. For sexually active individuals, a monogamous relationship with an uninfected partner is the best way to prevent genital HPV infection. Condom use reduces but does not eliminate the risk of sexual transmission of HPV.
Ireland

Ano-genital warts are notifiable in Ireland. The trend in notifications is similar in males and females (Figure 10.1).

**Figure 10.1** Anogenital wart notifications in Ireland by gender 1995-2014.

Source: HPSC

Note: the total also includes cases where the gender was unknown

The largest proportion of cases occurs in young adults in the 20-29 year age group (Figure 10.2).

**Figure 10.2**: Percentage of anogenital warts by age group 1995-2014.

Source: HPSC
Chapter 10 Human papillomavirus

A study of 996 cervical cytology samples in an Irish urban female, opportunistically screened population, found an overall HPV prevalence of 19.8%, HPV 16 at 20% and HPV 18 at 12% were the commonest high-risk types detected.

Cervical Cancer

Cervical cancer is the second most common cancer in women, with an estimated 445,000 new cases globally in 2012 and 270,000 deaths. Most cases occur in countries without effective screening programmes. In Ireland from 2011 - 2013, an average of 295 cervical cancers was diagnosed with 74 deaths per year. The average age at diagnosis was 45 years and at time of death 56 years. In addition, over 6500 in situ (CIN 1,2 and 3) cancers of the cervix are diagnosed annually. Incidence rates for in situ carcinoma of the cervix increased particularly from the mid/late 2000s when the cervical screening programme extended nationwide.

Figure 10.3 Rate of invasive and in situ cervical cancer per 100,000 population in Ireland, 1994-2013
Source: Irish Cancer Registry

Cervical screening can detect pre-cancerous lesions and cervical cancer at an early stage when treatment can be successful. In countries where there is an organised cervical cancer screening programme there has been a marked reduction in the incidence of invasive cervical cancer. Ireland’s National Cervical Screening Programme is CervicalCheck (www.cervicalcheck.ie).
History of HPV vaccination programme in Ireland

In September 2010 quadrivalent HPV vaccine (HPV4) was introduced routinely for all girls in first year of second level school and age-equivalent girls in special schools and those educated at home. Girls in second year and their age-equivalent counterparts who had not previously been targeted were also offered HPV4 vaccine.

In September 2011 a catch-up programme was introduced, with all girls in sixth year or equivalent from 2011 to 2014 offered HPV4 vaccine.

Human papillomavirus vaccines

Currently available HPV vaccines contain virus-like particles (VLPs) produced from the major capsid protein L1 of each HPV type using recombinant DNA technology. These vaccines are not live vaccines, contain no viral DNA and are not infectious or oncogenic.

Three HPV vaccines are licensed:
- a bivalent adjuvanted vaccine (HPV2) containing VLPs for HPV types 16 and 18 (Cervarix; GSK). HPV2 is licensed for females from the age of 9 years for the prevention of premalignant genital (cervical, vulvar and vaginal) lesions and cervical cancer causally related to HPV types 16 and 18.
- a quadrivalent adjuvanted vaccine (HPV4) containing VLPs for HPV types 6, 11, 16 and 18 (Gardasil; Sanofi Pasteur MSD). HPV4 is licensed for use from 9 years of age for the prevention of premalignant genital lesions (cervical, vulvar and vaginal), cervical cancer and external genital warts causally related to HPV types 6, 11, 16 and 18.
- a nonavalent vaccine (HPV9) containing VLPs for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 (Gardasil 9; Sanofi Pasteur MSD). HPV9 is licensed for use from 9 years of age for the prevention of premalignant genital lesions and cancers affecting the cervix, vulva, vagina and anus caused by vaccine HPV types, and external genital warts caused by specific HPV types.

HPV vaccines should be stored at +2 to +8°C. If a vaccine has been frozen it should not be used.

An up to date list of licensed vaccines can be accessed on the HPRA website www.hpra.ie

A list of the vaccines currently available from the national Cold Chain Service can be found at www.immunisation.ie
Immunogenicity and vaccine efficacy
All HPV vaccines are highly effective at preventing infection of susceptible women with the HPV types covered by the vaccines. HPV2 and HPV4 vaccines are over 99% effective in preventing pre-cancerous lesions associated with HPV types 16 and 18 in young women. Efficacy of HPV4 vaccine against HPV 6, 11, 16, or 18–related genital warts, is 99%.

Vaccination provides less benefit to females already infected with one or more of the HPV vaccine types. However, as prior infection with one vaccine type does not diminish vaccine efficacy against other types, vaccination can provide protection against those HPV vaccine types not previously acquired.

Protection lasts for at least nine years and is likely to be long-lasting. The need for a booster has not yet been determined.

Partial cross-protection has been demonstrated for both vaccines against infection with several non-vaccine oncogenic HPV types, including HPV 45 and 31 the commonest non-vaccine oncogenic types.

The use of vaccine does not eliminate the need for continued cervical cancer screening programmes, since between 10% and 30% of cervical cancers are caused by HPV types not included in the vaccine(s).

The impact of a population wide HPV4 vaccination programme has been demonstrated in Australia where there has been a 50% decline in high grade cervical abnormalities in girls under 18 years and a 93% reduction in the number of diagnoses of genital warts in women up to 21 years of age. In addition, there has been an 82% reduction in number of cases of genital warts diagnosed in heterosexual men up to 21 years of age: this decline can be attributed to the development of herd immunity.

HPV vaccines have been shown to produce the same or a higher degree of immunogenicity, and the same safety and reactogenicity in males compared with females of the same age. Even allowing for the impact of herd immunity from vaccinating girls, transmission would still be maintained through men who have sex with men.

Dose and route of administration
The dose is 0.5 ml by IM injection in the deltoid region. The number of doses depends on the age.

The recommended schedules and minimum intervals for HPV vaccines are shown in Table 10.1
**HPV2**

*For girls aged between 9 and 14 years (inclusive).*

Two doses administered at 0 and 6 months are recommended. If flexibility in the schedule is necessary, the second dose can be administered 5-7 months after the first dose. If the second vaccine dose is administered before the 5th month after the first dose, a third dose should be administered.

*For girls aged 15 years and older*

Three doses of vaccine, administered at 0, 1 and 6 months are recommended. If flexibility in the schedule is necessary, the second dose can be administered at 1-2.5 months, and the third dose at 5-12 months after the first dose.

There is no evidence to support a two dose schedule in those aged 15 and older.

**HPV4**

*For children aged between 9 and 14 years (inclusive)*

Two doses of vaccine, administered at 0 and 6 months are recommended. If the second vaccine dose is administered earlier than the minimum interval (24 weeks less 4 days) after the first dose, a third dose should always be administered at least three months after the second dose.

*For those aged 15 years and older*

Three doses of vaccine, administered at 0, 2 and 6 months, are recommended.

There is no evidence to support a two dose schedule in those aged 15 and older.

There is no evidence that the HPV2 and HPV4 vaccines are interchangeable. The same HPV vaccine should be used for the vaccination series. However, if the previously administered HPV vaccine is unknown or unavailable, either vaccine can be used to complete the series, to provide protection against HPV 16 and 18.

**HPV9**

*Aged 9-≤15 years:*

2-doses at 0, and 6 – 12 months for those who start the vaccination series before their 15th birthday. The two doses should ideally be separated by 6 to 12 months. The minimum interval between doses is 5 calendar months.

If the second dose is given <5 months after the first dose, a third dose should always be administered. This should be given 6–12 months after the first dose and at least 12 weeks after the second dose.
Chapter 10  Human papillomavirus

If one dose of HPV4 has been received, the 2-dose schedule can be completed with HPV9, as long as the first dose was given before age 15 years, and the second dose given at least 5 months after the first dose.

If the vaccination series is interrupted, the series does not need to be restarted.

**Aged 15 years of age and older:**
3 doses at 0, 2 and 6 months for females aged 15-<26 years, and MSMs aged up to 45 years of age. The second dose should be given at least one month after the first dose and the third dose should be given at least 3 months after the second dose. All three doses should preferably be given within a 1-year period.

The minimum interval between the first and second doses is 4 weeks. The minimum interval between the second and third doses is 12 weeks. The minimum interval between the first and third doses is 5 calendar months. If a dose is administered at less than the recommended minimum interval then the dose should be repeated.

If the vaccination series is interrupted, the series does not need to be restarted.

Those who have completed a course of HPV4 vaccination do not require revaccination with HPV9, unless they are at increased risk.

**Immunocompromising conditions**
(such as HIV infection, post-solid organ transplant): a 3-dose schedule is recommended (see Chapter 3).

Based on epidemiology studies, HPV9 vaccine is anticipated to protect against the HPV types that cause approximately 90% of cervical cancers, 85-90% of HPV related vulvar cancers, 80-90% of HPV related vaginal and vulvar cancers, 90-95% of HPV related anal cancer, and 90% of genital warts.
Table 10.1 Optimal age and intervals and minimum intervals for HPV vaccines

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number of doses</th>
<th>Dose 1 to Dose 2</th>
<th>Dose 2 to Dose 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Optimal interval</td>
<td>Minimum interval</td>
<td>Optimal interval</td>
</tr>
<tr>
<td>HPV2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9- &lt;15</td>
<td>2</td>
<td>6 months</td>
<td>5 months</td>
</tr>
<tr>
<td>15 and older</td>
<td>3</td>
<td>1 month</td>
<td>1 month</td>
</tr>
<tr>
<td>HPV4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9- &lt;15</td>
<td>2</td>
<td>6 months</td>
<td>24 weeks</td>
</tr>
<tr>
<td>15 and older</td>
<td>3</td>
<td>2 months</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

Indications

1. Females
All females at 12-13 years of age should receive HPV vaccine as part of the national HPV vaccination programme.

HPV vaccine may be given to females from 9 years age.

Females up to the age of 26 years may receive HPV vaccine. Ideally, the vaccine should be administered before potential exposure to HPV through sexual contact. Those who are sexually active should be advised that the vaccine has not been shown to have a therapeutic effect on existing HPV infection or cervical lesions.

HPV vaccines are generally not recommended for those over 26 years of age, because of lack of efficacy data. However, there is some evidence of efficacy for HPV4 vaccine in some women up to the age of 45 years so HPV4 vaccine should be considered for those individuals infected with HIV and for those who have had a haematopoietic stem cell transplant (see Chapter 3).

2. Males
HPV4 and HPV9 vaccines may be given to males from 9 to 26 years and should be considered for men who have sex with men (MSM), individuals infected with HIV and for those who have had a haematopoietic stem cell transplant.

3. Fanconi Anaemia
Patients with Fanconi Anaemia aged over 12 months should be offered HPV vaccine as soon as diagnosis is made due to their significantly increased risk of head, neck, oropharyngeal and anogenital squamous cell carcinoma. They should be given 3 doses of HPV4 or HPV9 vaccine with a 0, 2 and 6 month schedule.

Contraindications
Anaphylaxis to any of the vaccine constituents.
Chapter 10 Human papillomavirus

**Note:**
1. Those who have had a non-anaphylactic hypersensitivity reaction to HPV vaccine may be given a subsequent dose of that vaccine if indicated.
2. Yeast allergy is not a contraindication to the HPV4 vaccine. Even though the vaccine is grown in yeast cells, the final product does not contain any yeast.

**Precautions**
Acute severe febrile illness; defer until recovery.

Syncope has been reported among adolescents who received HPV or other vaccines, particularly in relation to administration of first dose. Recipients should be seated during vaccine administration.

**Pregnancy**
HPV vaccine is not recommended during pregnancy, although there is no known risk associated with using recombinant viral vaccines during pregnancy. If a woman becomes pregnant during the vaccination series, remaining doses should be delayed until after completion of the pregnancy.

**Use of HPV vaccine with other vaccines**
The vaccines can be given at the same visit as any other recommended vaccines.

**Adverse reactions**
*Local:* Pain, swelling and erythema are very common.

*General:* Fever ($\geq 38^\circ$), myalgia, headache and syncope are common.

**Note:** A review in 2015 by the European Medicines Agency of a possible association between HPV vaccines and Chronic Regional Pain Syndrome (CRPS), and Postural Orthostatic Tachycardia Syndrome (POTS) reported that the available evidence does not support a causative association between the HPV vaccines and CRPS or POTS. The report is available on the EMA website (www.ema.europa.eu).
Bibliography


Chapter 10  Human papillomavirus


