10 Human papillomavirus

Vaccine introduced to National Immunisation Schedule 2010 (girls); 2019 (girls and boys)
NOTIFIABLE

In some circumstances, advice in these guidelines may differ from that in the product Summary of Product Characteristics (SmPC). When this occurs, NIAC advises that the recommendations in these guidelines, which are based on current expert advice from NIAC, are followed.

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10.1 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). HPV infection has a causal role in cancers of the cervix, anus, penis, oropharynx, vulva and vagina. HPV is mainly transmitted through sexual contact; most infections occur shortly after the onset of sexual activity.

HPV is also responsible for a range of precancerous lesions and anogenital, oropharyngeal and cutaneous warts in men and women.

The HPV 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.

10.2 Epidemiology

Genital HPV infection is the most common sexually transmitted infection worldwide, although it is usually cleared by the immune system. The prevalence of cervical HPV infection in the pre-vaccine era varied from 2.4% to 47%, depending on age and region. A study of over 10,000 cases of invasive cervical cancer from 38 countries showed that the most common HPV types were 16, 18, 31, 33, 35, 45, 52, and 58; HPV types 16 and 18 represented 71% of cases. HPV 16 is twice as common as any other high-risk type except in sub-Saharan Africa where HPV 35 is equally common. Infection with one HPV type does not prevent infection with other types. Of those infected with genital HPV, 5-30% are infected with multiple types of the virus.

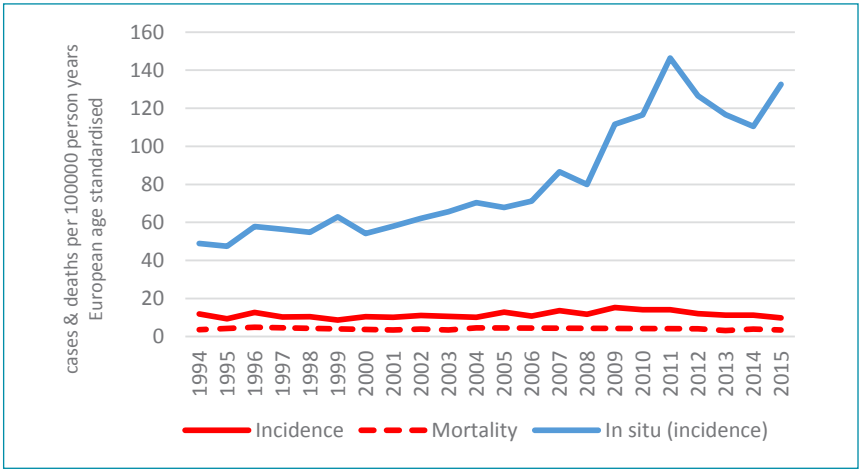
There are 13 **high risk types** (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68). Globally, these cause an estimated 530,000 cases of cervical cancer and 100,000 other cancers each year.

In Europe, types 16 and 18 cause over 70% of cervical cancers. HPV types 31, 33, 45, 52, and 58 are estimated to cause an additional 19%. 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 4.5% of the global cancer burden.

In 2018, approximately 311,000 women died from cervical cancer, more than 85% of these deaths occurring in low- and middle-income countries.

In Ireland, cervical cancer is the 8th most common cancer; there are 260 new cases of invasive cervical per year, with just under 3,000 cases of in-situ cancer.

Fig. 10.1 Cervical Cancer: cases and deaths per 100,000 person years (European age standardised) 1994-2015.
Source: National Cancer Registry of Ireland



Low-risk types 6 and 11 are associated with over 90% of genital warts and 10% of low grade cervical intraepithelial neoplasia (CIN1). 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. While anogenital warts are notifiable in Ireland, there is significant under-reporting. The trend in notifications is similar in males and females (Figure 10.2), although the numbers in males are more than twice those in females.

Figure 10.2: Anogenital wart notifications in Ireland by gender 1995-2017

Source: HPSC

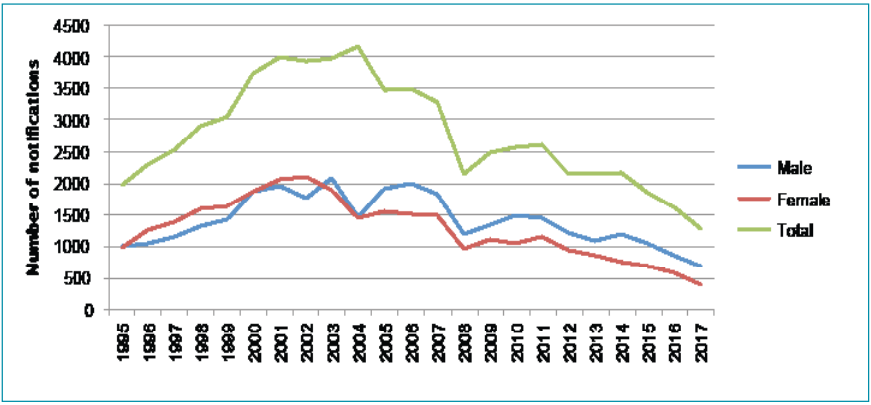
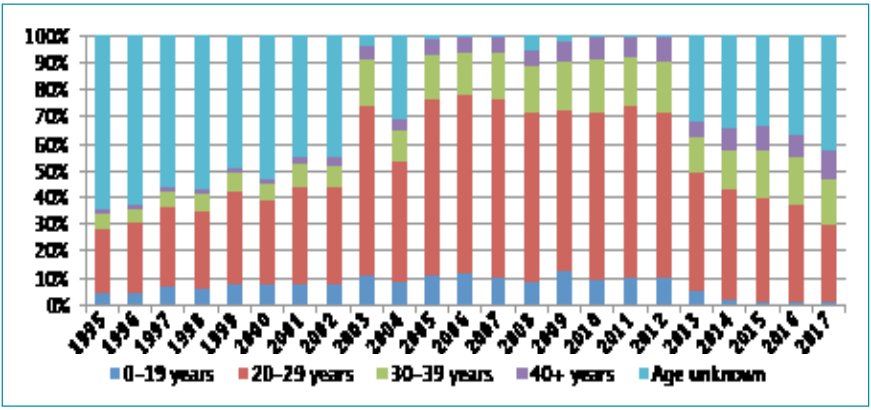


Figure 10.3: Percentage of anogenital warts by age group in Ireland 1995-2017

Source: HPSC



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 (20%) and HPV 18 (12%) were the commonest high-risk types.

Transmission occurs most frequently during vaginal, oral or anal sexual intercourse. Non-sexual routes of HPV transmission include transmission from mother to newborn baby, genital-to-genital, and hand-to-genital contact. Genital warts are highly contagious; two-thirds of those who have sexual contact with an infected partner develop warts.

Vertical transmission from mother to baby can cause juvenile recurrent respiratory papillomatosis.

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). The highest rates of HPV infection occur in the 18-28 year age group. An estimated 80% of sexually active women and men become infected with at least one type of HPV by age 50 years. Oral HPV infection is significantly more common in men, particularly men who have sex with men (MSM), than in women. Condom use reduces but does not eliminate the risk of sexual transmission of HPV.

10.3 Effects of HPV

HPV acquisition may result in asymptomatic infection, benign warts, pre-cancerous lesions, or invasive cancer.

Most genital HPV infections are asymptomatic and transient; 70% of new genital HPV infections clear within one year, and >90% within two years. High-risk types are more likely to result in persistent infection.

The most common clinically significant manifestation of persistent HPV infection is cervical intraepithelial neoplasia (CIN). Over a number of years, low-grade CIN (CIN1) may progress to high-grade CIN (CIN2 or CIN3). 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.

HPV infection also has a causal role in cancers of the anus, penis, oropharynx, vulva and vagina.

HPV is also responsible for a range of precancerous lesions and anogenital warts in men and women, and for juvenile recurrent respiratory papillomatosis.

HPV related cancers

There is a causal association between HPV and cancer of the cervix, vagina, vulva, oropharynx, anus and penis. Worldwide, cervical cancer is the fourth most frequent cancer in women (the eighth most commonly occurring cancer overall), with an estimated 570,000 new cases in 2018, and over 300,000 deaths. Approximately 90% of deaths from cervical cancer occurred in low- and middle-income countries. Most cases and deaths occur in countries without effective screening programmes.

In Ireland, from 2010 to 2014, an estimated average of 538 cases of HPV-associated cancers were diagnosed per year. Of these, 73% were in women. Cervical cancer was the most frequent HPV-associated cancer (292 cases per year). The next most frequent were oropharyngeal squamous cell carcinomas (133), squamous cell carcinomas of the vulva (38), penis (32), anus and rectum (31).

Oropharyngeal cancer accounts for 25% of all HPV-associated cancers. Cases have increased rapidly since 2014 in Ireland, mirroring international trends. Overall, 77.5% of all cases were in men, and approximately half are thought to be attributable to HPV.

Of all HPV-associated cancers, 360 cases per year were estimated to be directly attributable to HPV types contained in HPV9 vaccine.

Cervical screening can detect CIN 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).

HPV vaccination programme in Ireland

In September 2010 quadrivalent HPV vaccine (HPV4) was introduced for girls in first year of second level school and age-equivalent girls in special schools and those educated at home. Girls in second year or equivalent were also offered HPV4 vaccine.

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

In 2019, nonavalent vaccine (HPV9) was introduced into the national immunisation schedule for girls and boys in first year of second level school and age-equivalent students in special schools and those educated at home.

10.4 HPV vaccines

HPV vaccines are non-live vaccines containing virus-like particles (VLPs) prepared from surface proteins from constituent HPV types. VLPs are not infectious as they lack virus DNA. However, they closely resemble the virus and antibodies against the VLPs also have activity against the virus. The VLPs are strongly immunogenic.

Licensed indications

- *HPV2 (Cervarix, HPV 16, 18).* Indicated for use from the age of 9 years for the prevention of premalignant anogenital lesions (cervical, vulvar, vaginal and anal) and cervical and anal cancers causally related to HPV 16 and 18.
- *HPV4 (Gardasil, HPV 6, 11, 16, 18)*. Indicated for use from the age of 9 years for the prevention of:

  - premalignant genital lesions (cervical, vulvar and vaginal), premalignant anal lesions, cervical cancers and anal cancers causally related to the constituent HPV types
  - genital warts (*condyloma acuminata*) causally related to specific HPV types

- *HPV9 (Gardasil 9, HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58*). Indicated for active immunisation of individuals from the age of 9 years against the following HPV diseases:
  - premalignant lesions and cancers affecting the cervix, vulva, vagina and anus caused by the constituent HPV types.
  - genital warts (*Condyloma acuminata*) causally related to 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 authorised vaccines and SmPCs can be accessed on the HPRA website at 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 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%. HPV9 vaccine protects against the HPV types that cause approximately 90% of cervical cancers, 85-90% of HPV related vulvar cancers, 90-95% of HPV related anal cancer, and 90% of genital warts.

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

Fourteen year data from clinical trials shows no waning of immunity, and it is expected that the vaccines will provide long term protection.

The use of HPV vaccine does not eliminate the need for cervical cancer screening programmes, as 10 to 30% of cervical cancers are caused by HPV types not included in the vaccines.

Vaccine effectiveness

The impact of population wide HPV vaccination programmes has been demonstrated in a number of countries.

- In Scotland, 8 years after the introduction of HPV2 vaccine (3 doses in 12-13 year old girls) significant reductions were found in all grades of cervical intraepithelial neoplasia (CIN), equating to vaccine effectiveness estimates of ≥80%. Rates of CIN3+ decreased by 89%, CIN2+ by 88%, and CIN1 for those born in 1995-6 by 79%.
- In England (90% uptake), 8 years after the introduction of HPV vaccine, cancer-causing HPV infections had fallen 86% among women aged 16 to 21 eligible for the vaccine.
- In Australia, the HPV infection rate among women aged 18 to 24 dropped from 22.7% to 1.1% between 2005 and 2015.
- In Denmark, HPV4 vaccination was associated with a substantially lower risk of developing genital warts after an average of 3.5 years of follow-up.

Similar results are mirrored in other countries, including Finland, Japan, New Zealand, Norway, Sweden and the US.

If high-coverage universal HPV9 vaccination and cervical screening are maintained, modelling has shown that cervical cancer could be eliminated as a public health problem in Australia within the next 20 years.

The vaccine has not been shown to have a therapeutic effect on existing HPV infection or cervical lesions.

Data on the impact of HPV vaccine on oral disease is limited to studies demonstrating a reduction in oral HPV infection in vaccinated individuals. For example, HPV vaccination was associated with a significant reduction in vaccine-type oral HPV prevalence among young US males and females.

HPV vaccines are similarly effective and have a similar safety and reactogenicity profile in males and females of the same age.

Following one, two, or three vaccine doses, HPV antibodies reach an early peak followed by a decline to plateau around 18-36 months, and remain stable for at least 11 years.

There is now sufficient evidence that there is no significant difference in vaccine effectiveness between those aged nine to 24 years of age who are immunocompetent who receive one, two, or three vaccine doses.

For those aged 25 years and older and immunocompetent, available immunogenicity data provide sufficient evidence to support a two dose schedule.

There are insufficient data to support a one or two dose schedule for those with immunocompromise regardless of age.

Dose and route of administration
The dose is 0.5 ml by IM injection in the deltoid region. The number of doses depends on age. If the vaccination series is interrupted, the series does not need to be restarted.

HPV4 or HPV9
Age 9-24 years
A single dose of HPV vaccine is recommended.

Age 25 years and older
Two doses at 0 and 6-12 months.

If the second dose is given less than five months after the first dose, a third dose should be administered. This should be given 6–12 months after the first dose and at least 12 weeks after the incorrect second dose.

Immunocompromised
Those with the following conditions require a three dose schedule at 0, 2 and 6 months **regardless of age**.

- Haematopoietic stem cell or solid organ transplant recipients
- HIV infection
- Malignant haematological disorders affecting the bone marrow or lymphatic systems, e.g., leukaemia, lymphomas, blood dyscrasias
- Non-haematological malignant solid tumours
- Primary immunodeficiency
- Within two weeks of commencing on or within three to six months of receiving significant immunosuppressive therapy (see Chapter 3).

Revaccination
Revaccination with HPV9 of those who have completed a series with another HPV vaccine is not recommended as a routine. Clinicians should decide if the benefit of immunity against the five additional oncogenic strains of HPV, which cause 12% of HPV-attributable cancers, is justified for their patients.

The benefit of protection is mostly limited to females for prevention of cervical cancers and pre-cancers; only a small percentage of HPV-associated cancers in males are due to the five additional types prevented by HPV9.

Interchangeability
The same HPV vaccine should be used for the vaccination series. However, if the previously administered HPV vaccine is unknown or unavailable, any HPV vaccine can be used to complete the series.

10.5 Recommendations

10.5.1 Routine programme

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

10.5.2 Older children and adults

HPV catch-up vaccination is recommended for unvaccinated females and males under the age of 25 years. Second level students and females under the age of 25 years should be prioritised.

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.

10.5.3 Men who have sex with men (MSM)

HPV9 vaccine is recommended for MSM aged ≤45 years.

10.5.4 Immunocompromised persons (see also Chapter 3)

HPV9 vaccine is recommended for:

- Haematopoietic stem cell or solid organ transplant recipients aged ≤45 years
- HIV infected men and women aged ≤26 years
- HIV infected MSM aged ≤45 years
- Those with the following conditions:
  - Malignant haematological disorders affecting the bone marrow or lymphatic systems, e.g., leukaemia, lymphomas, blood dyscrasias
  - Non-haematological malignant solid tumours
  - Primary immunodeficiency
  - Within two weeks of commencing on or within three to six months of receiving significant immunosuppressive therapy (see Chapter 3).

10.5.5 Fanconi Anaemia

Patients with Fanconi Anaemia aged over 12 months should be offered HPV vaccine as soon as the diagnosis is made, due to their significantly increased risk of oropharyngeal and anogenital squamous cell carcinomas.

All immunocompromised persons should be given **3** doses of HPV9 vaccine at 0, 2 and 6 months, **regardless of age**.

10.5.6 For those who require excisional treatment of CIN lesions:

- HPV9 vaccine should be offered to previously unvaccinated women aged ≤45 years with CIN2+ lesions
- HPV9 vaccine may be offered to previously unvaccinated women aged ≤45 years with CIN1 lesions.

10.5.7 Children less than 12 years of age at risk of HPV exposure

HPV vaccine may be considered in children less than 12 years of age at risk of HPV exposure (e.g., with a history of sexual abuse or a sexually transmitted infection).

Contraindications

Anaphylaxis to any of the vaccine constituents.

Note:

- Those who have had a non-anaphylactic hypersensitivity reaction to HPV vaccine may be given a subsequent dose.
- Yeast allergy is not a contraindication to HPV4 or HPV9 vaccines. Although the vaccines are 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 before or following vaccination, particularly with the first dose. Recipients should be seated or lying down during vaccine administration.

Pregnancy

HPV vaccine is not recommended during pregnancy, although there is no known risk associated with using recombinant 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 with any other recommended vaccines, for instance MenACWY and Tdap. These should be given in the opposite limb to HPV vaccine.

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

General: Fever (≥38°C), headache, dizziness, nausea, fatigue, are very common or common. These generally resolve within 1-2 days. Syncope is uncommon.

There is no scientific evidence for a causal association between HPV vaccine and any long term medical condition including Chronic Regional Pain Syndrome (CRPS), Postural Orthostatic Tachycardia Syndrome (POTS) or Chronic Fatigue Syndrome.

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