

6a

Human papillomavirus

NOTIFIABLE

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. HPV targets basal cells in the stratified squamous epithelium and metaplastic cells at the squamocolumnar junction of the cervix and can, over time, lead to cervical cancer. Infection of the glandular epithelium of the endocervix can lead to adenocarcinoma. There are more than 100 different types of HPV. Some types are responsible for common warts (verrucae). Around 40 types can infect the genital tract. Genital infection is associated with genital warts and various cancers such as cancer of the cervix, vulva, vagina, anus, and penis. HPV infection is also associated with various oropharyngeal cancers in men and women. The types that cause genital warts (low-risk types e.g. HPV 6 and 11) are not those associated with cancer (high-risk types e.g. HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66).

Epidemiology

Genital HPV infection is the most common sexually transmitted disease worldwide. Transmission occurs during vaginal, oral or anal sexual intercourse or genital contact with an infected person. Non-

Chapter 6a Human papillomavirus

sexual routes of HPV transmission include vertical transmission from mother to newborn baby. The clinical spectrum of disease ranges from asymptomatic infection, to benign warts, to invasive cancer.

Genital warts are highly contagious; two-thirds of people who have sexual contact with an infected partner will develop warts. 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 HPV DNA assay. The highest rates of HPV infection occur in the 18-28 year age group. An estimated 80% of sexually active women become infected with at least one type of HPV by age 50 years.

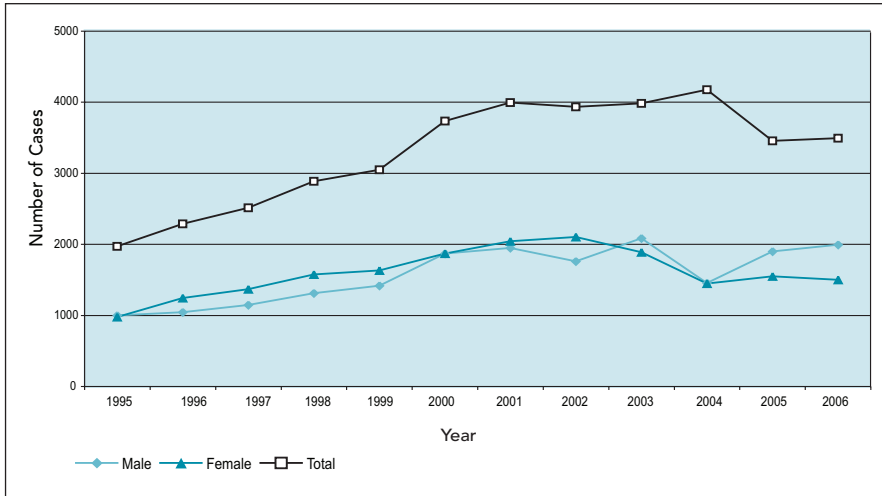
Most genital HPV infections are asymptomatic and transient. However, although 70% of new genital HPV infections clear within one year, and 91% within two years, high-risk types are more persistent than low-risk types. Persistent infection over a number of years may lead to grade 2 or 3 cervical intraepithelial neoplasia (CIN) and cervical cancer. In one study approximately 27% of women with an initial HPV 16 or 18 infection progressed to CIN2/3 within 36 months. Persistent infection by high-risk types is detectable in more than 99% of cervical cancers. Types 16 and 18 are responsible for over 70% of cervical cancers. Types 6 and 11 are associated with over 90% of genital warts.

The prevalence of cervical HPV infection varies worldwide. The International Agency for Research on Cancer (IARC) population-based studies found that overall HPV DNA prevalence varied 20-fold from 1.4% (95% CI 0.5-2.2) in Spain to 25.6% (95% CI 22.4-28.8) in Nigeria. The most common type was 16, followed by type 42, 58, 31, 18, 56, 81, 35, 33, and 45. HPV 16 was twice as common as any other high-risk type in all regions except sub-Saharan Africa where HPV 35 was equally common. Infection by multiple types was common.

Ireland

Ano-genital warts are notifiable in Ireland. They accounted for 35% of all sexually transmitted infection notifications in 2006. The trend in notifications is similar in males and females (Figure 1). The largest proportion of cases occurs in young adults in the 20-29 year age group.

Figure 1 Ano-genital wart notifications in Ireland by gender, 1995-2006.
Source: HPSC



Note: The total also includes notifications where gender was unknown

A recent study of 996 cervical cytology samples in an Irish urban female, opportunistically screened population, found an overall HPV prevalence of 19.8%, varying from 31% in women under 25, to 23% in women aged 25-35 and 11% in women over 35 years of age. HPV 16 at 20% and HPV 18 at 12% were the commonest high-risk types detected.

Effects of human papillomavirus

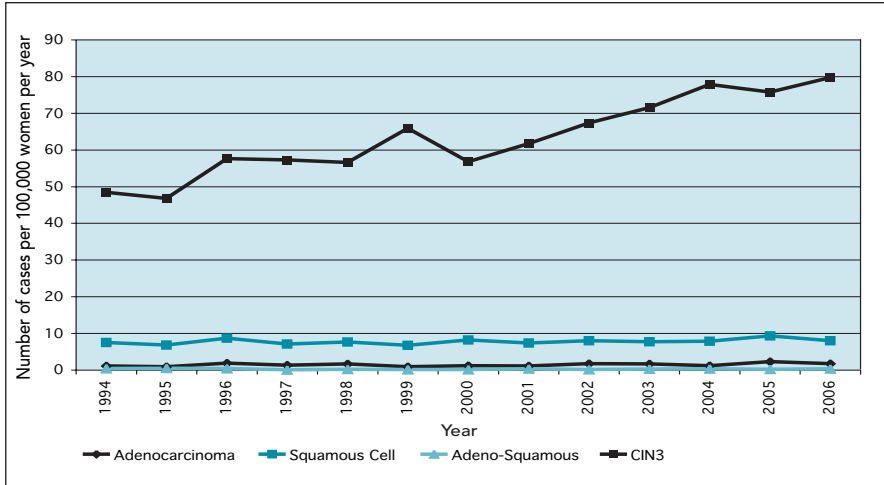
HPV is responsible for 5.2% of the cancer burden worldwide. Cervical cancer is the second most common cancer in women worldwide with an estimated 493,000 new cases in 2002 and 274,000 deaths. Most cases occur in countries without effective screening programmes.

In Ireland, on average 180 women develop cervical cancer each year with 73 deaths from cervical cancer. The average age at diagnosis is 46 years and of death is 56 years. Recent trends in the incidence of squamous cell carcinoma, adenocarcinoma, CIN3 and adeno-squamous carcinoma in Ireland are shown in Figure 2. The incidence of CIN3 has increased significantly from 1999 to 2006 while the incidence of carcinoma has remained unchanged.

Chapter 6a Human papillomavirus

Figure 2 Rate of invasive and in situ cervical cancer per 100,000 population in Ireland, 1994-2006.

Source: Irish Cancer Registry



Individuals can reduce their risk of getting genital HPV infection by changes in sexual behaviour including abstinence from any sexual activity or lifelong monogamy. Reducing the number of sexual partners and the frequency of new partners will also reduce the risk. Condom use reduces but does not eliminate the risk of sexual transmission of HPV.

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.

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. An up-to-date list of vaccines that are licensed and marketed in Ireland is contained in Appendix 1, or can be accessed on the IMB website at www.imb.ie. Full prescribing information relating to the HPV vaccines is available at www.medicines.ie.

Two HPV vaccines are licensed for use in Ireland, a bivalent vaccine containing VLPs for two HPV types (16 and 18) and a quadrivalent vaccine containing VLPs for four HPV types (6, 11, 16 and 18). The VLPs used in

the bivalent vaccine are adjuvanted by ASO4 containing 3-O-desacyl-4'-monophosphoryl lipid A (MPL) adsorbed on aluminium hydroxide. The VLPs used in the quadrivalent vaccine are adsorbed on amorphous aluminium hydroxyphosphate sulphate adjuvant.

Immunogenicity and vaccine efficacy

Both HPV vaccines are highly effective at preventing infection of susceptible women with the HPV types covered by the vaccines. Both vaccines were also found to be over 99% effective in preventing pre-cancerous lesions associated with HPV types 16 and 18 in young women. Efficacy of the quadrivalent vaccine against HPV 6, 11, 16 or 18-related genital warts was 99%. Vaccination provides less benefit to females if they have already been infected with one or more of the HPV vaccine types. Protection lasts for at least five years and is likely to be long-lasting. The need for a booster has not yet been determined for either vaccine. 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 vaccines will reduce but not eliminate the risk of cervical cancer since at present they target only two oncogenic HPV types (16 and 18) which account for 70% of cervical cancer risk. Therefore, cervical cancer screening programmes will continue to be important even in vaccinated populations.

Dose and route of administration

There is no evidence that the HPV bivalent and quadrivalent vaccines are interchangeable. If an individual has started a course of one vaccine then the vaccination series should be completed with that vaccine.

The bivalent vaccine is licensed for females aged 10-25 years for the prevention of premalignant cervical lesions (CIN2/3) and cervical cancer causally related to HPV types 16 and 18. Three doses (0.5ml) are recommended to be given at 0, 1 and 6 months by IM injection in the deltoid region.

The quadrivalent vaccine is licensed for females aged 9-26 years 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. Three doses (0.5ml) are recommended to be given at 0, 2 and 6 months by IM injection in the deltoid region. An alternative vaccination schedule may be used such that the second dose is given at least one month after the first dose and the third dose at least three months after the second dose with all three doses given within one year.

Chapter 6a Human papillomavirus

The vaccines are currently not licensed for women over 26 years of age or for males.

HPV vaccines should be stored at 2°C to 8°C in the original packaging and protected from light. If the vaccine has been frozen, it should not be used.

Indications

Recommendations for HPV immunisation:

- All girls 12 years of age should receive the vaccine
- It may be given to girls aged 9-12 years in accordance with the vaccine licence and at the discretion of the physician
- Females aged 13-26 years who would not have had the opportunity to receive the vaccine at age 12 may also be given the vaccine.

Ideally, the vaccine should be administered before potential exposure to HPV through sexual contact. However, as it is not possible to determine which females have been exposed to any or all of the HPV types contained in the vaccines, women in the appropriate age group with a history of sexual contact may also benefit from the vaccine. 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.

Contraindications

Anaphylactic reaction to a preceding dose or any of the constituents.

Precautions

Acute severe febrile illness; defer until recovery. The response may be impaired in those who are immunocompromised. Syncope has been reported among adolescents who received HPV or other vaccines. Recipients should be seated during vaccine administration. Where possible, patients should remain in the vicinity of the place of vaccination for up to 15 minutes.

Pregnancy and breastfeeding

HPV vaccine is not at present 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.

The quadrivalent vaccine can be given to breastfeeding mothers. The effect on breastfed infants of giving the bivalent vaccine to the mother has not been evaluated, although there is no known risk associated with using recombinant viral vaccines whilst breastfeeding.

Use of HPV vaccine with other vaccines

The vaccines can be given at the same visit as other vaccines recommended for persons of this age group (e.g. Tdap, MMR, hepatitis B, IPV), preferably in a different limb.

Adverse reactions

Local: Localised pain, swelling and erythema are very common at the injection site.

General: Fever ($\geq 38^\circ$), myalgia, fatigue and headache have been commonly reported. Fainting can uncommonly occur.

Bibliography

Ault KA (2006). Epidemiology and natural history of human papillomavirus infections in the female genital tract. *Infect Dis Obstet Gynecol*; Suppl: 40470.

Brown DR, Kjaer SK, Sigurdsson K, Iversen OE, et al (2009). The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in generally HPV-naive women aged 16-26 years. *J Infect Dis*; 199(7): 926-35.

Centers for Disease Control and Prevention (2008). Human papillomavirus. Epidemiology and prevention of vaccine preventable diseases. 10th edition. Atlanta, GA: Centers for Disease Control and Prevention.

Clifford GM, Gallus S, Herrero R, Munoz N, et al (2005). Worldwide distribution of human papillomavirus types in cytologically normal women in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis. *Lancet*; 366(9490): 991-98.

Department of Health (2006). Immunisation against infectious disease. 3rd edition. London: The Stationery Office.

FUTURE 11 Study Group (2007). Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med*; 356(19): 1915-27.

Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, et al (2007). Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med*; 356(19): 1928-43.

Harper DM, Franco EL, Wheeler C, Ferris DG, et al (2004). Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet*; 364(9447): 1757-65.

Harper DM, Franco EL, Wheeler CM, Moscicki AB, et al (2006). Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. *Lancet*; 367(9518): 1247-55.

International Agency for Research on Cancer (2007). Human papillomaviruses. IARC monographs on the evaluation of carcinogenic risks to humans, Volume 90. Lyons: International Agency for Research on Cancer.

Keegan H, Ryan F, Malkin A, Griffin M, Lambkin H (2007). Human papillomavirus prevalence and genotypes in an opportunistically screened Irish female population. *Br J Biomed Sci*; 64(1): 18-22.

Koutsky L (1997). Epidemiology of genital human papillomavirus infection. *American Journal of Medicine*; 102(5 Suppl 1): 3-8.

Koutsky LA, Galloway DA, Holmes KK (1988). Epidemiology of genital human papillomavirus infection. *Epidemiol Rev*; 10: 122-63.

Munoz N, Bosch FX, de Sanjosé S, Herrero R, et al (2003). Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med*; 348(6): 518-27.

Munoz N, Castellsague X, de Gonzalez AB, Gissmann L (2006). Chapter 1: HPV in the etiology of human cancer. *Vaccine*; 24 Suppl 3: S3-1-S310.

Myers ER, McCrory DC, Nanda K, Bastian L, Matchar DB (2000). Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. *Am J Epidemiol*; 151(12): 1158-71.

O'Hora A, Lambert J (2007). Human papillomavirus in Ireland. Health Protection Surveillance Centre.

Oriel J (1971). Natural history of genital warts. *Br J Vener Dis*; 47: 1-13.

Paavonen J, Jenkins D, Bosch FX, Naud P, et al (2007). Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind randomised controlled trial. *Lancet*; 369(9580): 2161-70.

Parkin DM (2006). The global health burden of infection-associated cancers in the year 2002. *Int.J Cancer*; 118(12): 3030-44.

Parkin DM, Bray F, Ferlay J, Pisani P (2005). Global cancer statistics, 2002. *CA Cancer J Clin*; 55(2): 74-108.

Chapter 6a Human papillomavirus

Smith JS, Lindsay L, Hoots B, Keys J, et al (2007). Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. *Int J Cancer*; 121(3): 621-32.

Stanley M (2008). HPV vaccines: are they the answer? *Br Med Bull*; 88(1): 59-74.

Villa LL, Costa RL, Petta CA, Andrade RP, et al (2006). High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. *Br J Cancer*; 95(11): 1459-66.

Wheeler CM, Kjaer SK, Sigurdsson K, Iversen OE, et al (2009). The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in sexually active women aged 16-26 years. *J Infect Dis*; 199(7): 936-44.

Winer RL, Kiviat NB, Hughes JP, Adam DE, et al (2005). Development and duration of human papillomavirus lesions, after initial infection. *The Journal of Infectious Diseases*; 191(5): 731-38.

Women's Health Council and National Cancer Registry Ireland (2006). Women and cancer in Ireland, 1994-2001. Cork: National Cancer Registry.

World Health Organization (2009). Human papillomavirus vaccines: WHO position paper. *Weekly Epidemiological Record*; 15: 118-31.