

HUMAN PAPILLOMAVIRUS VACCINES FOR AUSTRALIANS: INFORMATION FOR GPs AND OTHER IMMUNISATION PROVIDERS

Summary

- Genital human papillomavirus (HPV) is a common and usually asymptomatic infection. Transmission of genital HPV occurs largely via sexual contact. It is highly contagious and many people will acquire an HPV infection within a few years of becoming sexually active. Most people clear that HPV infection within 12–24 months.
- Of the 40 genital HPV types, 15 are classified as 'high risk' types, of which two (16 and 18) are most common. High risk types can establish persistent cervical infection which in turn can result in cervical abnormalities which, in rare cases, will progress to cervical cancer. Infection with HPV is necessary, though not sufficient, for development of cervical cancer.
- HPV vaccines are prophylactic only and will not treat existing HPV infection or disease.
- Two HPV vaccines are available in Australia, the quadrivalent HPV vaccine, Gardasil[®], and the bivalent HPV vaccine, Cervarix[®]. Both vaccines provide 90–100% protection against persistent infection and cervical/genital disease due to HPV types 16 and 18 (which cause 70–80% of cervical cancers in Australia). Gardasil[®] is approved for use in females aged 9–26 years. Cervarix[®] is approved for use in females aged 10–45 years.
- As part of the National Immunisation Program (NIP), the Australian Government is providing the HPV vaccine through a school-based program and a community-based program. To be eligible for free vaccine provided by the community-based HPV catch-up program, all females ages 12–26 years must have started the course with their first dose of the vaccine on or before 30 June 2009, and complete all three doses by 31 December 2009. After December 31 2009, HPV vaccination will continue to be provided under the NIP for girls 12–13 years of age in high school based immunisation programs. Both Gardasil[®] and Cervarix[®] are now provided free of charge under the National HPV Vaccination Program. Decisions regarding the choice of HPV vaccine used are made at the state/territory program level.
- Sexually active women who are vaccinated will, at an overall population level, derive less protection than women who receive the vaccine prior to commencement of sexual activity.
- The most important preventive strategy against cervical cancer for women who are sexually active is Pap screening every two years. Women who have received a HPV vaccine still require two-yearly Pap screening because the vaccine does not provide protection against all HPV types.
- Both Gardasil[®] and Cervarix[®] are generally safe and well tolerated. The most common side effect is a local reaction at the site of the injection.
- There is currently no data available on the interchangeability of the two HPV vaccines. It is recommended that an HPV vaccination course which commences with one vaccine should be completed with that vaccine if possible.
- HPV vaccines are not routinely recommended or funded for use in males at this time in Australia.
- The National HPV Vaccine Register has been established to support the HPV Vaccination Program, and assist in ongoing monitoring and evaluation. The Register will receive data from all states and territories and from all types of vaccination providers.

Human papillomavirus

Human papillomaviruses (HPVs) are small, non-enveloped DNA viruses. HPVs infect and replicate within cutaneous and mucosal epithelial tissues, most commonly involving the skin or anogenital tract. HPVs are designated as specific types according to sequence variation in the major genes.

There are approximately 40 HPV types designated as mucosal/genital types. Of these, some 15 HPV types are designated as 'high risk' types, which are causally associated with the development of cervical cancer (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82).¹ These HPV types have also been associated with the development of some anal cancers, vaginal and vulval cancers, penile cancers, and head and neck cancers. Of the low risk genital HPV types, types 6 and 11 are important causes of genital warts (causing approximately 95% of genital warts).²

Transmission of genital HPV occurs largely via sexual contact. There is a high probability of transmission following sexual exposure to a person with HPV infection, estimated to be 50–80% following unprotected sexual intercourse.^{3–5} HPV infection is often subclinical but, dependent upon the infecting HPV type, may result in lesions that include cutaneous warts, genital warts, cervical and other anogenital tract abnormalities and cancers, and respiratory papillomatosis.

Current understanding of natural history of cervical dysplasia

It was originally thought that there was an inevitable progression from low grade cervical abnormalities to high grade abnormalities to cervical cancer. It is now recognised that Low-grade Squamous Intraepithelial Lesion (LSIL) cytology is a manifestation of acute HPV infection, and that most LSILs regress over time.³ Most genital HPV infections are cleared (no longer detectable) within 12–24 months (median duration oncogenic types 7–10 months);^{6–9} in a minority (estimated at 3–10%) the virus persists,¹⁰ which can result in cervical abnormalities which, in rare cases, will progress to cervical cancer. Infection with HPV is necessary, though not sufficient, for development of cervical cancer.

Epidemiology of HPV infection in women

HPV infection rates vary greatly between geographic regions and population groups, but it is estimated that up to 79% of women worldwide will be infected with HPV at some point in their lives.^{11,12} HPV infection rates are highest among young women, usually peaking soon after the age when most young women become sexually active.¹³ Prospective studies in the USA and UK have indicated high rates of HPV acquisition in young women (eg. among women aged 14–20 years, 10–32% acquire HPV16 and 4–20% HPV18 infection over 2–4 years).^{14–16} A woman's lifetime number of sex partners is the most important predictor of HPV acquisition. In a study of monogamous women, 48% acquired HPV infection within three years of becoming sexually active despite only having one partner.¹⁷

Epidemiology of HPV related cervical disease

Every year in Australia, Pap testing detects low grade cervical abnormalities in about 90,000 women and high grade cervical abnormalities in a further 15,000 women. The incidence of both low and high grade abnormalities peaks in women aged 20–24 years.³

Australia has one of the lowest rates of incidence and mortality from cervical cancer in the world.¹⁸ There were 718 new cases in Australia in 2004 (6.9 per 100,000 women of all ages). The age-standardised mortality rate from cervical cancer was 1.9 deaths per 100,000 women in 2005.¹⁹ This low incidence is due to the success of the National Cervical Screening Program. Regular Pap testing allows the early detection and treatment of HPV related cervical abnormalities prior to the development of cervical cancer. In Australia, there are about 720 cases, 1800 hospitalisations and 215 deaths each year from cervical cancer. Cervical cancer in Australia now occurs predominately in unscreened or under-screened women. Indigenous women have more than double the risk of developing cervical cancer and a mortality rate over four times that of non-Indigenous women.¹⁹

Human papillomavirus vaccines

Successfully applied molecular biology techniques have underpinned the development of prophylactic HPV vaccines. It is of critical importance to note that HPV vaccines are prophylactic, that is, designed to prevent initial HPV infection. They are not therapeutic vaccines. When given as a three dose series, HPV vaccines elicit antibody titres many times higher than those observed in natural infection.²⁰⁻²² It should be noted that there is currently no standard serological assay for detecting HPV antibodies and no protective titre has been established.

Overall, seroconversion occurs in 99–100% of those vaccinated.²⁰⁻²² The duration of immunity from vaccination is not yet known as long-term follow-up studies are ongoing. It is at least five years duration,^{21,22} but booster doses may be required.

Quadrivalent HPV vaccine

Gardasil[®] (CSL Biotherapies/Merck & Co Inc) is a recombinant protein particulate quadrivalent HPV vaccine (types 16, 18, 6 and 11) registered in Australia for use in females aged 9–26 years and in males aged 9–15 years. The cost for a privately purchased course of immunisation with Gardasil[®] (ie. three doses) is approximately \$460.

The dose of Gardasil[®] is 0.5 mL administered intramuscularly. The recommended schedule is for three doses administered at 0, 2 and 6 months. Where flexibility in the recommended dosing schedule is unavoidable, the second dose can be administered at least one month after the first dose and the third dose can be administered from at least three months after the second.

Bivalent HPV vaccine

Cervarix[®] (GlaxoSmithKline) is a recombinant protein particulate bivalent HPV vaccine (types 16 and 18). It was registered for use in females aged 10–45 years in Australia at an approximate cost of \$450 per three dose course (private purchase).

The dose of Cervarix[®] is 0.5 mL administered intramuscularly. The recommended schedule is for three doses administered at 0, 1 and 6 months. The second dose can be administered between one and 2.5 months after the first dose.

Both Gardasil[®] and Cervarix[®] are now provided free of charge for certain groups under the National Immunisation Program (NIP). Gardasil[®] was added to the NIP in April 2007 and Cervarix[®] was added in October 2008. Decisions regarding the choice of HPV vaccine used are made at the state/territory program level.

Efficacy

Gardasil[®] is highly effective (>90%) when given prophylactically to women who are uninfected with the HPV types covered by the vaccine (types 16, 18, 6 and 11) prior to completion of a three dose vaccination course. In women who are HPV DNA negative and HPV seronegative for relevant types, Gardasil[®] is highly effective at preventing persistent type-specific infection, cervical disease and external genital lesions (~90–100%)^{20,22-25}

Analysis of trial data indicate that when vaccine effectiveness (VE) is considered for all women, regardless of baseline HPV status, the overall impact of the vaccine is much lower. At a mean of three years follow-up of all women enrolled in Gardasil[®] trials who received at least one dose of vaccine, efficacy against high grade cervical intraepithelial neoplasia (CIN2/3) or worse due to types 16 or 18 was 44% (31–55%) and against high grade CIN caused by any HPV type was 18% (7–29%).²⁴ Similarly, in an analysis of 5500 women who received at least one dose, the effectiveness against external genital lesions was also lower for HPV types 6/11/16/18 related disease, at 73% (58–83%), and for disease due to any type, at 34% (15–39%).²⁵ This reflects the fact that some women were already persistently infected with HPV types covered by the vaccine and, in these women, HPV vaccine did not prevent disease. In addition, a large number of other HPV types cause cervical abnormalities which are more likely to spontaneously regress than types 16 and 18 (thus resulting in a larger number of cancers caused by 16 and 18 than by other types).

As demonstrated in a phase II study,^{21,26} and early results from a phase III trial,²⁷ Cervarix[®] is highly effective (>90%) when given prophylactically to women who are uninfected at baseline with the relevant HPV type (16 or 18) covered by the vaccine. In the phase II study of women who were HPV DNA negative and HPV seronegative for relevant types, Cervarix[®] was highly effective at preventing persistent type-specific

infection and cervical disease (90–100%). Similarly, in women who were baseline negative to relevant types in the phase III study and received at least one vaccine dose, efficacy against type specific CIN was high (83–100%).

Thus, both vaccines are best administered prophylactically to females who are not yet sexually active and, therefore, unlikely to be infected with HPV.

Pre-adolescent males and females have a good immune response to vaccination, producing antibody levels at least twice as high as those in women in whom clinical efficacy has been demonstrated.

Cross protection against non-targeted HPV types

Trial data suggest that HPV vaccines provide some, although far from complete, protective efficacy against infection and disease due to types closely related to types 16 and 18. Follow-up of an initially HPV naïve trial population vaccinated with the bivalent vaccine indicates some protection against incident infection with HPV31 (VE 60%; 95% confidence intervals [CI] 21%–81%) and HPV45 (VE 78%; 95% CI 39%–93%).²⁸ In an analysis of quadrivalent vaccine trial participants who had received at least one dose of vaccine and were HPV naïve at baseline, there was some protection against HPV31 related CIN (VE 70%; 95% CI 32%–88%).²⁹

Who should be vaccinated?

Vaccine eligibility under the National Immunisation Program

The National Immunisation Program providing free HPV vaccination to females aged 12–26 years commenced in April 2007. The program provides free vaccination to (1) an ongoing target group of 12 and 13 year old girls (delivered in the first year of high school through a school-based program); (2) a catch-up group of 13–18 year old girls (largely delivered in a school-based program); and (3) women aged 18–26 years (delivered through general practice and community-based programs). The latter two programs are catch-up programs which are funded until December 2009. However, to be eligible for free vaccine, all females in the above age groups must have started the course with their first dose of vaccine on or before 30 June 2009, and complete all three doses by 31 December 2009.

Routine vaccination of females in the first year of high school will continue indefinitely. Eligibility is from the first year of secondary school in your state or territory at 12 or 13 years of age. Program information is available at: <http://www.health.gov.au/cervicalcancer>.

Vaccination for other women

The following factors may be considered when discussing the benefit of HPV vaccination for a woman not eligible for funded vaccine under the NIP.

As indicated earlier, HPV vaccines have their highest efficacy when given to females who are not already infected with those HPV types targeted by the vaccine. The only fully reliable indicator of no previous infection with HPV is no prior sexual activity. Of note, first sexual intercourse is reported at a median age of 16 years by Australian women and men.³⁰

At the individual level, the primary factor which influences the likelihood of benefit from HPV vaccine is the number of sexual partners. However, even women with a high probability of HPV infection (ie. multiple sexual partners) are unlikely to have past or current infection with *all four* HPV types covered by the quadrivalent vaccine. An Australian serosurvey in 2005 indicated that by the age of 30–39 years, 27% of women had antibodies to either HPV16 or 18, with 6% having antibodies to both types, and 1% having antibodies to all four types.³¹ Because of the limited sensitivity of HPV serology, these percentages represent a minimum estimate of the percentage of women who have been infected with these types by this age. There is currently no data available to indicate at what rate new infections with HPV16 or 18 occur in women over 26 years of age in the Australian population. A recent Australian review discusses in more detail some of the issues in considering the costs and benefits of HPV vaccination for individual women aged over 26 years.³² The potential benefit derived from HPV vaccination can vary in women older than 26 years.

Pre-immunisation screening with HPV DNA tests* is not warranted, as the information obtained from these tests is not specific to the vaccine types, and will not tell you whether the woman has natural immunity to HPV.

* Routine HPV testing is not eligible for a Medicare Benefits Schedule rebate except in determining test of cure for women undergoing treatment of a high grade squamous intraepithelial lesion of the cervix.

Vaccine recipients will still require Pap tests as the vaccine does not prevent all HPV types which can cause disease. In sexually active women, the most important preventive intervention against cervical disease remains regular Pap smears. Vaccination is NOT an acceptable alternative to Pap smears. The National Cervical Screening Program recommends routine screening with Pap smears every two years for all women between the ages of 18 (or two years after first sexual intercourse) and 69 years. Screening in older women may be indicated.

Vaccine use in men

Routine HPV vaccination of males is not recommended in Australia at the present time and the vaccine is not funded for use in males.

Recently released trial data indicate that the quadrivalent vaccine is efficacious in males against persistent infection (VE 86%; 95% CI 75%–92%)³³ and external genital lesions, largely genital warts, (VE 90%; 95% CI 69%–98%) due to vaccine targeted types.³⁴ Results from ongoing vaccine trials assessing the prevention of anal intraepithelial neoplasia in men who have sex with men are awaited.

National HPV Vaccination Program Register (The HPV Register)

The HPV Register has been established to monitor and evaluate the HPV Vaccination Program. The Register will receive data from all states and territories and from all types of vaccination providers. The HPV Register will record data about HPV vaccine doses administered, select demographic data, and data on the person who administers the vaccine.

If you are a general practitioner and have administered a HPV vaccine dose to an eligible female, you are eligible for a payment of \$6.00 for each notification to the HPV Register. Detailed information about the Register can be found at <http://www.hpvregister.org.au>.

Safety

Both Gardasil® and Cervarix® are generally safe and well tolerated. HPV vaccines are approved for use in over 100 countries.

The main side effect of the vaccines is local reactions at the injection site (pain, redness and swelling) which occur in about 80% of vaccine recipients. All of the available data to date, both in the vaccine trials and in clinical usage, indicate that the vaccine is very safe. The vaccine has been evaluated for safety and efficacy by the Food and Drug Administration (FDA) in the USA, the Therapeutic Goods Administration (TGA) in Australia and the European Medicines Agency (EMA), all of which have concluded that the vaccine is safe and effective.

Vaccines require clinical testing in greater numbers than most other clinical drugs in order to meet regulatory conditions for approval. HPV vaccine trials for Gardasil® involved around 33,000 people worldwide. Safety information was collected on over 13,000 individuals who received HPV vaccine. In addition, over 40 million doses have been distributed worldwide and over 4.5 million doses distributed in Australia to date. The other HPV vaccine, Cervarix®, has been tested in similar numbers. These studies were large enough to detect adverse reactions occurring as infrequently as one in several thousand.

Post-marketing surveillance data has indicated that anaphylaxis can occur rarely following administration of Gardasil®. This is not unexpected as anaphylaxis is a very rare, but known, side effect following other types of vaccines as well. If a hypersensitivity reaction (such as generalised urticaria or angioedema) is reported to have occurred in close temporal association with a previous vaccine dose, careful clinical review and vaccination only under close clinical supervision is indicated.

Although serious reactions appear uncommon, all patients should be observed for 15 minutes post vaccination. Updated HPV adverse events surveillance data reports can be found at <http://www.tga.gov.au/alerts/medicines/gardasil.htm>.

Interchangeability of HPV vaccines

There is currently no clinical data available on the interchangeability of the two HPV vaccines approved for use in the National Immunisation Program. However, from first principles, there is no reason to suppose that acceptable antibody levels against HPV 16 and 18 (the types that cause cervical cancer) would not be produced using a combination schedule. It is recommended that an HPV vaccination course which commences with one vaccine should, wherever possible, be completed with that vaccine.

However, where the course includes a combination of the two HPV vaccines, either inadvertently or intentionally, the person shall be considered to be fully immunised if a total of three doses of HPV vaccine has been given, provided the appropriate minimum inter-vaccine dose intervals have been met.

Co-administration with other vaccines (HepB, varicella, dTpa)

Gardasil[®] has been administered at the same time as hepatitis B vaccine in clinical trials (at a separate site and in a separate syringe) with no reduction in immunogenicity of either vaccine observed. A randomised controlled trial showed that co-administration of quadrivalent HPV vaccine and HepB vaccine was well-tolerated and induced a robust immune response to both vaccines.³⁵ Co-administration of HPV vaccine and the adult/adolescent formulation of diphtheria-tetanus-acellular pertussis (dTpa) vaccine has been shown to be non-inferior to separate administration of the two vaccines.³⁶

Although there is no trial data available, there is no reason to believe that HPV vaccines cannot be administered on the same occasion as other vaccines such as varicella.

Contraindications and precautions

- HPV vaccine should not be given to anyone who has hypersensitivity to any component of the vaccine (including yeast for Gardasil[®]) or who has had an anaphylactic reaction to a previous dose.
- HPV vaccine should not be administered during pregnancy. If vaccination is inadvertently received during pregnancy, the rest of the vaccination course should be deferred until after pregnancy. Inadvertent HPV vaccination is not an indication for termination of pregnancy.
- As recommended for all vaccines, HPV vaccine should not be given during any moderate to severe febrile illness.

Responding to questions about HPV vaccine

Please see the NCIRS fact sheet 'Quadrivalent HPV vaccine – frequently asked questions' (http://www.ncirs.usyd.edu.au/facts/hpv_faq.pdf) for information to assist providers in answering patient concerns about the vaccine.

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