

Human papillomavirus (HPV)

HUMAN PAPILLOMAVIRUS (HPV) VACCINES FOR AUSTRALIANS: INFORMATION FOR IMMUNISATION PROVIDERS

This fact sheet provides information on HPV disease and the available vaccines, to assist immunisation providers in the delivery of HPV vaccinations. It can be used in conjunction with the NCIRS fact sheet [Quadrivalent HPV vaccine – frequently asked questions](#), which provides responses to common patient questions and concerns about the vaccine.

Disease and epidemiology

- Genital human papillomavirus (HPV) is a common sexually transmitted infection in both males and females. Most people will acquire an HPV infection within a few years of becoming sexually active.
- The majority of genital HPV infections are asymptomatic and are cleared within a year. A small proportion of HPV infections persist in the genital epithelium where they can lead to abnormalities in the cells. In rare cases, these abnormalities progress, usually over many years, to cancer.
- Cancers caused by HPV infection include cancer of the cervix, vagina, vulva, penis and anus. HPV infection is also associated with some cancers of the head and neck.
- There are many types of HPV. Of the 40 mucosal HPV types known, HPV types 16 and 18 are the most common causes of HPV-associated cancers. Some HPV types are not associated with cancer, for example, HPV types 6 and 11 are the types that commonly cause genital warts.

Who should be vaccinated

- HPV vaccine is included in the Australian National Immunisation Program (NIP) and is routinely provided via school-based programs for girls and boys 12–13 years of age. Catch-up vaccination is available for males aged 14–15 years in 2013 and 2014. Vaccination is given in a 3-dose course.
- Those who receive the vaccine prior to commencement of sexual activity will gain the most benefit from HPV vaccine.
- The National HPV Vaccination Program Register assists in ongoing monitoring and evaluation. All vaccination providers should report doses given to the Register.

Vaccines

- Two HPV vaccines are available in Australia: the quadrivalent HPV vaccine, Gardasil[®], which protects against four HPV types – 16, 18, 6 and 11; and the bivalent HPV vaccine, Cervarix[®], which protects against two HPV types – 16 and 18. Gardasil is the only HPV vaccine currently registered in Australia for use in males.
- Both vaccines provide 90–100% protection against persistent infection and cervical/genital disease due to HPV types 16 and 18 in females. Gardasil[®] also provides greater than 85% protection against persistent genital infection and disease due to vaccine HPV types in males.
- Both Gardasil[®] and Cervarix[®] are safe and generally well tolerated. The most common side effect is a local reaction at the site of the injection.
- Vaccination does not prevent infection from all HPV types. Therefore, Pap tests remain an important preventive strategy against cervical cancer for women.

The disease

Human papillomaviruses (HPVs) are small, non-enveloped DNA viruses. HPVs infect and replicate within cutaneous and mucosal epithelial tissues. There are 40 HPV ‘types’ which infect the mucosal epithelium classified according to sequence variation in the major genes.

Transmission of genital HPV occurs largely via sexual contact. There is a 50–80% chance of HPV transmission following unprotected sexual intercourse with a person with a current HPV infection.¹⁻³ The majority of genital HPV infections are subclinical and resolve spontaneously, clearing (i.e. no longer detectable) within 12–24 months of initial infection. Depending on the infecting HPV type, a small proportion of HPV infections can persist (estimated at 3–10%),⁴ resulting in cellular abnormalities and, in a subset of cases, precancerous disease; a subset of these progress into cancer. The progression from mucosal HPV infection to cancer can take many years.

Of the mucosal HPV types, 15 are designated as ‘high-risk’ types, due to their causal association with the development of cervical cancer (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82).⁵ These HPV types are also associated with the development of other cancers in females and males, including vaginal, anal and penile cancers, and head and neck cancers. An infection with HPV is necessary for the development of the associated cancers; however, an HPV infection on its own is not enough for cancer development as not all HPV infections progress to cancer.⁶

Of the genital HPV types considered to be ‘low risk’, types 6 and 11 are major causes of genital warts (causing approximately 95% of genital warts) and recurrent respiratory papillomatosis.⁷

Epidemiology of HPV infection and associated disease

HPV infection rates vary greatly between geographic regions and population groups, but it is estimated that around 80% of the general population will be infected with HPV at some point in their lives.^{8,9} HPV infection rates are highest among young women, usually peaking soon after the age when most young women become sexually active.¹⁰ However, in men, HPV infection is evident at all ages and the risk of acquiring new HPV infection seems to remain stable over time.¹¹ A person’s lifetime number of sex partners is a significant predictor of HPV acquisition although HPV is frequently acquired from a first and only sexual partner.¹²

The largest burden of HPV-associated cancers in Australia is attributable to cervical cancer. Prior to the introduction of HPV vaccination of females, every year in Australia Pap testing would detect low-grade cervical abnormalities in about 90,000 women and high-grade cervical abnormalities in a further 15,000 women. However, since the HPV vaccination program began in 2007, a reduction in the incidence of high-grade cervical abnormalities has been observed, suggesting early impact of the vaccination program.¹³

Prior to vaccine introduction, due to the success of the National Cervical Screening Program, Australia had relatively low rates of incidence and mortality from cervical cancer, particularly compared with less developed countries in the world.¹⁴ In 2007, the age-standardised incidence rate of cervical cancer in Australia was 6.8 per 100,000, and the mortality rate was 1.8 deaths per 100,000 women. Cervical cancer in Australia now occurs predominantly in unscreened or under-screened women. Indigenous women have more than double the risk of developing cervical cancer and a mortality rate 5 times that of non-Indigenous women, an indication of both lower participation rates in cervical screening programs and greater prevalence of cofactors for cervical cancer.^{15,16} The incidence and mortality rates of other HPV-associated cancers in women (vaginal, vulvar and anal) are lower than for cervical cancer.

The burden of HPV-associated cancers in males in Australia is less than that in women; however, HPV-associated cancer incidence in males, particularly for anal and tonsillar cancers, has been increasing in recent decades while remaining relatively stable in females. Men who have sex with men (MSM) are at particularly high risk of HPV-associated disease. The estimated incidence of anal cancer in MSM in Australia is greater than that of cervical cancer in women prior to the introduction of cervical screening program.¹⁷ There are no systematic screening programs in place for HPV-associated disease in males because there is currently limited evidence to support secondary prevention for these conditions.¹⁸

Who should be vaccinated

National Immunisation Program

The National Immunisation Program (NIP) provides free HPV vaccination to females and males aged 12–13 years, delivered through schools. A short-term catch-up program is being offered in 2013 and 2014 to males in either Year 9 or Year 10 (either 14 or 15 years of age) depending on the state or territory. Males who are aged 15 years in 2013 and are in the school year above that in which HPV

vaccine is being delivered are able to receive the vaccine free of charge from their general practitioner or community health clinic. Detailed information on the HPV vaccination program in each state and territory is available at the HPV School Vaccination Program website: www.australia.gov.au/hpv.

Others recommended for vaccination

A number of factors should be considered when discussing the benefit of HPV vaccination for a male or female not eligible for funded vaccine under the NIP. An assessment of the potential benefits of vaccination should be based on likely previous HPV exposure and future risks of HPV exposure.

HPV vaccines have their highest efficacy when given to those who are not already infected with the HPV types targeted by the vaccine. At the individual level, the primary factor which influences the likelihood of previous exposure to HPV, and in turn potential benefit from HPV vaccine, is the number of sexual partners. Therefore, older individuals would be more likely to have been previously exposed to HPV through sexual contact. However, even persons with a higher probability of HPV infection (i.e. multiple sexual partners) are unlikely to have past or current infection with *all four* HPV types covered by the quadrivalent vaccine and may potentially gain some benefit from vaccination.¹⁹

Pre-immunisation screening with HPV DNA tests* or by serologic testing is not warranted. Information obtained from these tests is not specific to the vaccine types and will not indicate whether a person has natural immunity to HPV.

HPV vaccination may be beneficial for adult men and women who are immunocompromised due to certain medical conditions (including HIV infection) or medical treatments. Being immunocompromised increases the risk of persistent HPV infection and subsequent progression from infection to disease. The decision to vaccinate immunocompromised persons should take into account their likelihood of previous exposure to HPV, their future risks of HPV exposure, and the extent and duration of their immunocompromise.

Men who have sex with men are at increased risk of HPV infection and associated disease (independent of HIV status or the presence of other immunocompromising conditions) and are less likely to benefit from herd

immunity attained from HPV vaccination of females. Decisions to vaccinate men who identify as MSM should take into consideration their likelihood of previous exposure to HPV and their future risks of HPV exposure.

Vaccines

The two available HPV vaccines both contain virus-like particles (VLPs) which are made using recombinant vaccine technology; they are not live vaccines. HPV vaccines are prophylactic, that is, designed to prevent initial HPV infection. They are not therapeutic vaccines and will not clear an existing HPV infection. When given as a 3-dose series, HPV vaccines elicit antibody titres many times higher than those observed in natural infection.²⁰⁻²² However, there is no routine diagnostic serological assay for detecting HPV antibodies. No protective antibody threshold has been established, and serologic testing before or after vaccination is not required.

Quadrivalent HPV vaccine

Gardasil® (bioCSL/Merck & Co Inc.) is a quadrivalent VLP HPV vaccine (types 16, 18, 6 and 11) registered in Australia for use in females aged 9–45 years and in males aged 9–26 years.

Bivalent HPV vaccine

Cervarix® (GlaxoSmithKline) is a bivalent VLP HPV vaccine (types 16 and 18). It is registered in Australia for use in females aged 10–45 years. Cervarix® is not registered for use in males of any age.

For females, Gardasil® was added to the NIP in April 2007 and Cervarix® was added in October 2008.

Gardasil® was added to the NIP for males commencing February 2013. Currently only Gardasil® is provided free of charge under the National Immunisation Program. Either vaccine can be accessed privately.

Administration

The dose of Gardasil® and Cervarix® is 0.5 mL administered intramuscularly.

The recommended schedule for Gardasil® is 3 doses administered at intervals of 0, 2 and 6 months. The recommended schedule for Cervarix® is 3 doses administered at intervals of 0, 1 and 6 months.

The minimum acceptable interval for HPV vaccines is 4 weeks between doses 1 and 2, and 12 weeks between doses 2 and 3. Contact your local state or territory health department for guidance if HPV vaccine has been given within the recommended minimum interval. See also the Chief Medical Officer Guideline available at

* 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.

www.health.gov.au/internet/immunise/publishing.nsf/Content/cmo-full-advice-hpv-cnt, or the 10th edition of *The Australian Immunisation Handbook* (www.immunise.health.gov.au).

If scheduled doses have been missed, earlier doses should not be repeated. The missed dose(s) should be given as soon as is practicable.

Vaccine efficacy/effectiveness

The efficacy of both HPV vaccines has been extensively assessed in clinical trials enrolling females. In women who are naïve to (i.e. have never been infected with) the vaccine HPV types, 3 doses of Gardasil® is highly effective (~90–100%) at preventing persistent type-specific infection, cervical disease and external genital lesions associated with HPV types 6, 11, 16 and 18.^{20,22–25} Similarly, Cervarix® is highly effective at preventing persistent vaccine HPV type-specific infection and cervical disease (90–100%).

Gardasil® has been shown to be immunogenic in males 9–26 years of age, with efficacy demonstrated in a clinical trial enrolling males aged 16–26 years.²⁶ Vaccination prevented more than 85% of persistent anogenital infections and external genital lesions due to vaccine HPV types among HPV-naïve participants. In a subset of participants who were men who have sex with men, vaccine efficacy was 95% against intra-anal HPV infection and 75% against high-grade anal intraepithelial neoplasia from vaccine HPV types.

When vaccine efficacy is assessed in all clinical trial participants, regardless of baseline HPV status, the overall impact of the vaccine is lower, indicating reduced vaccine effectiveness in persons who are sexually active. For example, in a pooled analysis of the efficacy of Gardasil® in women 16–26 years age, vaccination prevented 98.2% (93.3–99.8%) of high-grade cervical lesions (CIN2 or worse) associated with vaccine HPV types in women who were naïve to vaccine HPV types prior to vaccination. However, for all women enrolled in the trials (including those who were already infected with the vaccine HPV types), the overall efficacy of the vaccine against high-grade cervical lesions associated with vaccine HPV types was lower at 51.5% (40.6–60%). This highlights that vaccination will not clear an existing HPV infection or prevent disease that may be caused by an existing HPV vaccine-type infection, hence the importance of vaccinating prior to HPV exposure.^{22,27,28}

In clinical trials of males and females, overall, seroconversion to HPV vaccination occurs in 99–100% of those vaccinated.^{20–22} The lifetime duration of immunity

from vaccination is not yet known. However, antibody persistence to at least 9 years has been demonstrated in females.²⁹ Pre-adolescent males and females have a good immune response to vaccination, producing antibody levels at least twice as high as those in women and men in whom clinical efficacy has been demonstrated.^{30,31}

Cross-protection against non-targeted HPV types

In clinical trials enrolling females, both vaccines have demonstrated some cross-protection against non-vaccine HPV types phylogenetically related to HPV 16 and 18.³² The level of protection varies between HPV types and is much lower than observed with vaccine HPV types. For example, in women aged 16–26 years who were HPV naïve, Gardasil® reduced the incidence of HPV31/45 infection by 40.3% (95% CI: 13.9–59.0%) and of HPV31/45 CIN1–3/AIS (adenocarcinoma in situ) by 43.6% (95% CI: 12.9–64.1%).³³ A study of Cervarix® in women aged 15–25 years, who were naïve to relevant HPV type at baseline, demonstrated vaccine efficacy of 84.3% (95% CI: 59.5–95.2%) and 59.4% (95% CI: 20.5–80.4%) for CIN2+ due to HPV31 and HPV33, respectively.³⁴

Vaccine safety

HPV vaccines are approved for use in over 100 countries, with more than 100 million doses distributed worldwide. Extensive clinical trial and post-marketing safety surveillance data indicate that both Gardasil® and Cervarix® are well tolerated and safe.

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. Meta-analyses on pooled data from multiple clinical trials on both HPV vaccines have shown no increase in the risk of serious adverse events among vaccine recipients compared with control/placebo recipients.^{35,36} No deaths reported in safety surveillance systems data in Australia or overseas, have been determined to be causally related to either of the HPV vaccines.

Post-marketing surveillance data have indicated that anaphylaxis can occur rarely following administration of Gardasil®. If a hypersensitivity reaction (such as generalised urticaria or angioedema) is reported to have occurred in close temporal association (usually hours or a few days) with a previous vaccine dose, careful clinical review and possibly re-vaccination under close clinical supervision is indicated.

Health professionals should report any adverse events following HPV immunisation via the method in place in their relevant state or territory. More information on

reporting adverse events following immunisation, including contact information, can be found in the 10th edition of *The Australian Immunisation Handbook* (www.immunise.health.gov.au)

Adverse event reports for Gardasil® can be found on the TGA website (www.tga.gov.au/safety/alerts-all.htm) and HPV adverse events are included in annual national adverse events reports published in *Communicable Diseases Intelligence* (available at www.health.gov.au/internet/main/publishing.nsf/Content/cda-aefi-anrep.htm).

Concomitant administration with other vaccines

Gardasil® has been assessed in clinical trials when delivered concomitantly (at the same visit but in a separate site with a separate syringe) with: reduced antigen content diphtheria-tetanus-acellular pertussis vaccine (dTpa); diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine (dTpa-IPV); meningococcal serogroups A, C, Y and W₁₃₅ polysaccharide diphtheria toxoid conjugate vaccine (4vMenCV); and hepatitis B vaccine (monovalent).³⁷⁻⁴¹ Co-administered vaccines are well tolerated and induced a robust immune response that is not inferior to when either vaccine is delivered on its own.³⁹

There are no clinical data regarding concomitant administration of either HPV vaccine with varicella vaccine, but there are no theoretical concerns about safety or efficacy of the vaccines if they are given simultaneously, using different injection sites.

Interchangeability

There are currently no clinical data available on the interchangeability of the two HPV vaccines approved for use in Australia. 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 3 doses of HPV vaccine has been given, provided the appropriate minimum inter-vaccine dose intervals have been met.

Contraindications/precautions

HPV vaccine should not be given to anyone who has experienced an anaphylactic reaction to any component of the vaccine (including yeast for Gardasil®) or following a previous dose of vaccine.

HPV vaccine should not be administered during pregnancy. If vaccination is inadvertently administered during pregnancy, the rest of the vaccination course should be deferred until after pregnancy. Females who inadvertently receive a dose of HPV vaccine around the time of conception or during pregnancy should be informed that the scientific evidence suggests there is no harm to the pregnant woman or her fetus if vaccination has occurred inadvertently during pregnancy. For more information on vaccine safety during pregnancy see the 10th edition of *The Australian Immunisation Handbook* (see www.immunise.health.gov.au).

As recommended for all vaccines, HPV vaccine should not be given during any moderate to severe febrile illness.

Other considerations

Cervical screening in women who have been vaccinated

As HPV vaccines only protect against four HPV types, regular Pap tests are still recommended as per national guidelines for women who have received HPV vaccine. In sexually active women, the most important preventive intervention against cervical disease remains regular Pap tests. Vaccination is *not* an 'alternative' to Pap tests; together these two approaches provide optimal protection. The National Cervical Screening Program recommends routine screening with Pap tests every 2 years for all women between the ages of 18 (or 2 years after first sexual intercourse) and 69 years. See www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/cervical-about for more information.

National HPV Vaccination Program Register (the 'HPV Register')

The HPV Register has been established to monitor and evaluate the HPV Vaccination Program. The HPV Register collects data about HPV vaccine doses administered, select demographic data, and data on the person who administers the vaccine.

General practitioners and other immunisation providers are strongly encouraged to notify all HPV vaccine doses administered to the HPV register. This ensures patient records of vaccination are up to date and provides a resource which immunisation providers can check to confirm a patient's vaccination history. The register also sends reminder notices and completion statements to vaccinated persons (or their parents/guardians) and will facilitate notification to the patient if it is ever identified in the future that a booster dose is required. It also ensures accurate coverage statistics are available for program

evaluation and monitoring. Detailed information about the HPV Register can be found at www.hpvregister.org.au.

Responding to questions about HPV vaccine

Please see the NCIRS fact sheet [Quadrivalent HPV vaccine – frequently asked questions](#) for information to assist providers in answering patient concerns about the vaccine.

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