

# HUMAN PAPILLOMAVIRUS VACCINES FOR AUSTRALIANS: INFORMATION FOR GPS AND IMMUNISATION PROVIDERS

## Summary

- Genital human papillomavirus (HPV) is a common and usually asymptomatic infection. 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 (in about 3–10% of infected women) which in turn can result in cervical abnormalities which, in some cases, will progress to cervical cancer.
  - HPV vaccines are prophylactic only and will not treat existing HPV infection or disease.
  - One prophylactic HPV vaccine is currently available in Australia. Gardasil<sup>®</sup> (given in a three dose schedule at 0, 2 and 6 months) provides 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) and HPV types 6 and 11 (which cause 90% of genital warts). Another HPV vaccine, Cervarix<sup>®</sup>, which will provide protection against HPV types 16 and 18, is expected to become available in 2007.
  - Gardasil<sup>®</sup> is approved for use in females aged 9 to 26 years. Vaccine will be provided free of charge to all women 12–26 years through either school-based programs or general practice commencing in 2007.
  - Sexually active women up to 26 years who are vaccinated will, overall, derive less protection than when the vaccine is given prior to sexual activity. Currently available laboratory tests are not able to determine type-specific HPV infection, so pre-immunisation screening is not warranted.
  - The most important preventive strategy against cervical cancer for women who are sexually active is two yearly Pap screening. Women who have received a HPV vaccine still require two yearly Pap screening, because the vaccine does not provide protection against all HPV types.
  - Gardasil<sup>®</sup> is approved for use in males aged 9 to 15 years, based on the demonstration of safety and HPV antibody responses in males. However, as yet there is no data demonstrating that the vaccine is effective in preventing HPV infection, genital warts or other genital lesions in males.
- Gardasil<sup>®</sup> is generally well tolerated, with a small increase in injection site reactions and fever compared to placebo.

## 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).<sup>1</sup> 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 90% of genital warts).<sup>2</sup>



Transmission of genital HPV occurs largely via sexual contact. There is a high probability of transmission following sexual exposure to a person with a productive HPV infection, estimated to be 50–80% following unprotected sexual intercourse.<sup>3-5</sup> 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. Most genital HPV infections are cleared (no longer detectable) within 12–24 months (median duration oncogenic types 7–10 months),<sup>6-9</sup> in a minority (estimated at 3–10%) the virus persists.<sup>10</sup> Most of the host immune response is directed against the two proteins of the viral capsid, L1 and L2.

### Epidemiology of HPV infection in women

HPV infection rates vary greatly between geographic regions, but it is estimated that up to 79% of women worldwide will be infected with HPV at some point in their lives.<sup>11-12</sup> HPV infection rates are highest among young women, usually peaking soon after the age when most young women become sexually active.<sup>13</sup> 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).<sup>14-16</sup> A woman's lifetime number of sex partners is the most important predictor of HPV acquisition.

### Epidemiology of HPV related cervical disease

Every year in Australia, Pap testing detects low grade cervical abnormalities in ~90,000 women and high grade cervical abnormalities in a further 15,000 women.<sup>3</sup> The incidence of both low and high grade abnormalities peaks in women aged 20–24 years. It was originally thought that there was an inevitable progression from low grade 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 LSIL regresses over time.<sup>3</sup>

Australia has the second lowest incidence rate of cervical cancer and the lowest mortality rate among developed countries with comparable cancer registration systems.<sup>3,17</sup> In 2002, the age standardised incidence rate in Australia was 6.8 per 100,000 and in 2004, the mortality rate 1.9 per 100,000.<sup>18</sup> 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 750 cases, 1800 hospitalisations and 250 deaths each year from cervical cancer. Cervical cancer in Australia now occurs predominately in unscreened or under-screened women.

### Type-specific HPV epidemiology

Worldwide, approximately 70% of cervical cancers contain either HPV16 or HPV18 DNA.<sup>1,19</sup> HPV16 or HPV18 have been detected in 52% of high grade cervical lesions, 25% of low grade cervical lesions and 3% of cytologically normal women.<sup>20-22</sup>

Australian studies indicate that HPV16 and 18 are responsible for about 77% of cervical cancers here<sup>23-27</sup> and about 45% of high grade cervical abnormalities.<sup>23,24</sup>

### Human papillomavirus vaccines

Successfully applied molecular biology techniques have underpinned the development of prophylactic HPV vaccines. In 1991, Zhou et al reported that the major HPV capsid protein, L1, can self assemble into virus-like particles (VLPs) when independently expressed in eukaryotic cells by recombinant DNA technology.<sup>28</sup> This discovery led to the development of HPV vaccines based on type-specific VLPs. VLPs lack any viral oncogenes and are not infectious.

It is of critical importance to note that VLP based HPV vaccines are prophylactic, that is designed to prevent initial HPV infection. They are not therapeutic vaccines, designed to clear existing infection or HPV related disease. When given as a three dose series, HPV vaccines elicit antibody titres many times higher than those observed in natural infection. Antibody responses peak at month 7 (one month after dose three) at between 7 and 150 times natural infection levels depending upon the HPV type and vaccine, and appear to plateau at 18–24 months.<sup>29-31</sup> It should be noted that there is no standard serological assay for detecting HPV antibodies and no protective titre has been established.

Overall, seroconversion occurs in 99–100% of those vaccinated.<sup>29-31</sup> The duration of immunity from vaccination is not yet known. It is at least five years duration,<sup>30,31</sup> but booster doses may be required.



Gardasil<sup>®</sup> (CSL Limited/Merck and Co, Inc) is a quadrivalent HPV vaccine registered for use in Australia in 2006 and available on the private market since August 2006. It is registered for use in females aged 9–26 years and in males aged 9–15 years. The cost for a course of immunisation with Gardasil<sup>®</sup> is approximately \$460. In late November 2006, the Australian Government announced that Gardasil<sup>®</sup> will be funded for three groups under the National Immunisation Program commencing in 2007. These groups comprise (1) an ongoing target group of 12 and 13 year old girls (delivered in the first year of high school) (2) a catch-up group of 13–18 year old girls (largely delivered in a school based program) and (3) women aged 18 to 26 years (to be delivered through general practice and community based programs) as a catch up for two years. For further information about the proposed immunisation program see [http://www.health.gov.au/internet/wcms/publishing.nsf/Content/gardasil\\_hpv.htm](http://www.health.gov.au/internet/wcms/publishing.nsf/Content/gardasil_hpv.htm)

Cervarix<sup>®</sup> (GlaxoSmithKline) is a bivalent HPV vaccine containing the major capsid (L1) protein of HPV16 and 18. It is expected to become available in Australia in 2007.

Gardasil<sup>®</sup> contains the major capsid (L1) protein of HPV types 6, 11, 16 and 18 at doses of 20, 40, 40 and 20 mcg respectively. The L1 proteins are produced by separate fermentations in recombinant *Saccharomyces cerevisiae* CANADE 3C-5 (Strain 1895) (a yeast) and self-assembled into VLPs. VLPs are purified and adsorbed on aluminium-containing adjuvant (amorphous aluminium hydroxyphosphate sulphate). The vaccine is a sterile liquid suspension (0.5 mL) containing 225 mcg of aluminium adjuvant, 9.65 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, and water for injection.

The dose of Gardasil<sup>®</sup> is 0.5 mL administered intramuscularly. The recommended schedule is for three doses administered at 0, 2 and 6 months.

### Efficacy

Gardasil<sup>®</sup> is highly effective 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 HPV DNA negative and HPV seronegative for relevant types, Gardasil<sup>®</sup> is highly effective at preventing persistent type-specific infection, cervical disease and external genital lesions (~90–100%)<sup>29,31</sup> Thus the vaccine is best administered prophylactically to females who are not yet sexually active and, therefore, unlikely to be infected with HPV.

Analysis of trial data indicate that when vaccine effectiveness is considered for all women, regardless of baseline HPV status, the overall impact of the vaccine is much lower. In all women enrolled in Gardasil<sup>®</sup> trials who received at least one dose of vaccine, efficacy against high grade cervical intraepithelial neoplasia (CIN) due to types 16 or 18 was 36.3% (19.4–49.9%) and against high grade CIN caused by any HPV type was 12.2% (<0–25.3%). Similarly, the effectiveness against external genital lesions was also lower for 6/11/16/18 related disease 70.4% (61.0–77.7%) and due to any type 39.8% (27.5–50.1%).<sup>31</sup> 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).

There is currently no clinical efficacy data available in men or in pre-adolescent females. Antibody response to vaccination has been evaluated in these groups. Young males and females produce antibody responses at least as high as women in whom clinical efficacy has been demonstrated.

### Who should be vaccinated?

As indicated above, 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, with first sexual intercourse reported at a median of 16 years by Australian women.<sup>32</sup> In males, no data regarding the clinical efficacy of HPV vaccines are expected before 2008.



Gardasil® is approved for use in females in Australia aged 9 to 26 years and for males aged 9 to 15 years. At the individual level, the primary factor which influences the likelihood of benefit from HPV vaccine is 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.

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.

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 (every two years) 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.

### Use in men

Although the vaccine is registered for use in males aged 9 to 15 years, HPV vaccination of males is not recommended at this time due to an absence of clinical efficacy data. Whilst HPV vaccine produces high antibody titres in males, it is not known whether HPV vaccination of males can prevent transmission of HPV or provide protection against genital HPV infection, genital warts, anogenital dysplasia or anogenital cancers.

### Safety

Gardasil® is generally well tolerated, with a small increase in reports of injection site reactions and fever compared to aluminium containing placebo (injection site reactions 83% vs 73%, fever 13% vs 11%). Very few serious adverse reactions were reported in the clinical trials.

### Co-administration with other vaccines (Hep B, 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. Although there is no trial data available, there is no reason to believe that human papillomavirus vaccines cannot be administered on the same occasion as other vaccines such as varicella or adult diphtheria-tetanus-pertussis vaccine.

### Contraindications

- Human papillomavirus 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.

Human papillomavirus vaccine should not be administered during pregnancy.

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

\* 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.



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