

## 3.7 HUMAN PAPILLOMAVIRUS

### Virology and HPV classification

Human papillomaviruses (HPVs) are small, non-enveloped viruses that have circular double-stranded DNA. 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 40 distinct HPV genotypes that affect the genital tract; of these, 15 genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82) are designated as 'high-risk' as they are causally associated with the development of cervical cancer. HPV genotypes 16 and 18 are the causative agents in 70 to 80% of all cervical cancers. HPV genotypes 6 and 11 are among the HPV genotypes designated as 'low-risk' (for cancer), and are associated with 90% of genital warts and 100% of recurrent respiratory papillomatosis (RRP) cases.<sup>1,2</sup>

High-risk genital HPV genotypes are associated with a spectrum of other anogenital diseases, including vulval, vaginal, penile and anal cancers, and their precursors. In addition, genital HPV genotypes are associated with extragenital diseases, including some squamous cell carcinomas of the head and neck (high-risk HPV types) and recurrent respiratory papillomatosis (HPV types 6 and 11).

Persistent HPV infection is a necessary precursor of cervical cancer, but is not sufficient in itself to cause the disease.<sup>3</sup> For pre-cancerous lesions to form and progress to cancer, the crucial event appears to be HPV DNA integration into the host cell genome, which interferes with the expression and regulation of proteins responsible for normal cell growth and repair.<sup>4</sup> Malignancy due to build-up of sufficient mutations for cellular transformation usually requires 10 to 20 years, but has been reported to occur in under 2 years.<sup>5</sup>

### Clinical features

HPV infection is often subclinical but, dependent upon the infecting HPV genotype, may result in lesions that include cutaneous warts, genital warts, cervical and other anogenital tract dysplasias and cancers, and respiratory papillomatosis. Most genital HPV infections are cleared (no longer detectable) within 12 to 24 months (the median duration for high-risk genotypes is 7 to 10 months).<sup>6-9</sup> In a minority of infections, estimated at 3 to 10%, the virus persists.<sup>10</sup>

## Epidemiology

### HPV infection

Transmission of HPV occurs through contact with infected skin or mucosal surfaces, primarily via sexual contact for the genital HPV genotypes. Transmission may rarely occur by other mechanisms, such as laryngeal infection of infants during birth.<sup>11</sup> There is a high probability of transmission following sexual exposure to a person with a productive HPV infection, estimated to be 50 to 80%, after unprotected sexual intercourse.<sup>12-14</sup> However, sexually active adolescents and young adults may remain naïve to all 4 vaccine HPV genotypes or be infected with a non-vaccine HPV genotype.

HPV infection rates vary greatly between geographic regions, but it is estimated that up to 79% of women worldwide will be infected with at least one genital type of HPV at some point in their lives.<sup>15,16</sup> HPV infection rates are highest among young women, usually peaking soon after the age when most young women become sexually active.<sup>17</sup> Australian data show that, among women currently aged 16–19 years, the median age of first intercourse is 16 years.<sup>18</sup>

Although comprehensive risk-prediction models for HPV exposure are not available, an increasing number of lifetime sex partners is consistently found to be associated with HPV acquisition.<sup>19-24</sup> A US population-based study of women aged 18–25 years found genital HPV infection in 14.3% of women with one lifetime sex partner, 22.3% with 2 lifetime sex partners, and 31.5% with more than 3 lifetime partners.<sup>25</sup> Australian women aged 16–19 years report a median number of 2 lifetime sexual partners, women aged 20–29 years a median of 4.3 lifetime sexual partners, and those aged 30–39 years a median of 4.7 lifetime sexual partners.<sup>26</sup> Although its sensitivity is somewhat limited, HPV seroprevalence measured using serum anti-HPV antibody levels can be used to estimate cumulative lifetime exposure to specific types of HPV infection.<sup>27</sup> In a study of women in Finland, Dillner et al (1996) described a linear increase in the risk of HPV16 seropositivity of 4% for every additional sex partner, ranging from 4% for 1 lifetime partner to 35% among those with 6 or more partners.<sup>24</sup> Similarly, HPV18 seroprevalence was observed to increase linearly at the rate of 3% per partner from 4% for 1 lifetime partner up to 24% for 6 or more partners. In the US, population data indicate that 25% of women aged 20–29 years are seropositive for HPV16.<sup>28</sup> An increasing number of sexual contacts on the part of their male partner is also associated with HPV acquisition in women.<sup>29</sup>

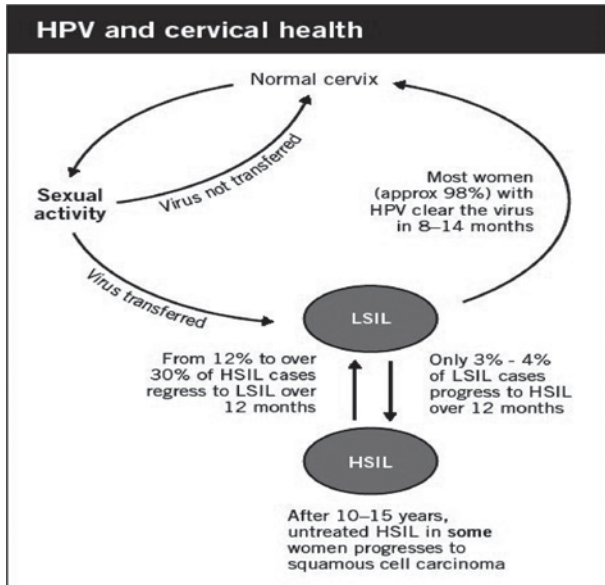
## Cervical abnormalities

Cervical infection with HPV causes a range of pathological responses depending on the genotype of HPV. These range from no reaction, carriage of HPV without cytological changes, to a variety of cellular changes in the cervix. Histologically, the cervical abnormalities have been referred to as cervical intraepithelial neoplasia (CIN), with 3 grades of severity: CIN1 (mild dysplasia), CIN2 (moderate dysplasia) and CIN3 (severe dysplasia/carcinoma in situ). CIN3 and AIS (adenocarcinoma in situ) are immediate precursors of cervical cancer. CIN2 represents a mix of low-grade and high-grade lesions (and hence it is treated as a high-grade lesion). Cytologically, under the Australian Modified Bethesda System, the term Low-grade Squamous Intraepithelial Lesion (LSIL) encompasses changes thought to be due to HPV and mild dysplasia, and the term High-grade Squamous Intraepithelial Lesion (HSIL) encompasses the former categories of moderate dysplasia, severe dysplasia and carcinoma in situ. Guidelines for the interpretation and treatment of screen-detected cervical abnormalities are published by the NHMRC.<sup>12</sup>

Every year in Australia, approximately 90 000 women have an LSIL detected and 15 000 women have an HSIL detected through Pap screening.<sup>12</sup> The incidence of both lesions peaks in women aged 20–24 years. In addition, there are approximately 20 000 hospital admissions per year for cervical dysplasia and carcinoma in situ. This is an underestimate of the burden of disease, as the investigation and management of cervical lesions are mostly carried out as outpatient procedures, either in the private or public sector. For procedures in the private sector, Medicare has processed, over the past 10 years, claims for an average of approximately 104 000 examinations of the lower genital tract by colposcopy and 14 600 combined colposcopy procedures per year. As well as physical side effects and complications from treatment for cervical abnormalities, there is consistent evidence that receipt of an abnormal Pap smear result, and the subsequent investigation and management, is associated with a considerable psychosocial burden.<sup>30–35</sup>

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 LSIL cytology is a manifestation of acute HPV infection, and that most LSIL regresses over time.<sup>12</sup> The absolute risk of cancer associated with a high-grade abnormality is difficult to determine from available observational data, but is estimated at less than 1% per year.<sup>36</sup> Figure 3.7.1 summarises the dynamic relationship between HPV infection and cervical health.

Figure 3.7.1: The dynamic relationship between HPV infection and cervical health



(Figure courtesy of the Australian Government Department of Health and Ageing.)

### Cervical cancer

Cancer of the uterine cervix is the second most common cause of cancer among women worldwide.<sup>37</sup> However, Australia has one of the lowest mortality rates from cervical cancer in the world.<sup>38</sup> In 2002, the age standardised incidence rate in Australia was 6.8 per 100 000 and, in 2004, the mortality rate was 1.9 per 100 000, with an estimated 750 cases, 1800 hospitalisations and 250 deaths each year from cervical cancer.<sup>39</sup> This low incidence can be attributed to the success of the National Cervical Screening Program, with cervical cancer in Australia now occurring predominantly in unscreened or under-screened women. The largest decline in cervical cancers has been observed for those of squamous origin, with the incidence of adenocarcinomas being essentially unchanged. This has been attributed to sampling difficulties in obtaining cells from the area where adenocarcinoma arises, problems in pathological interpretation, and variations in clinical investigation and treatment.<sup>12</sup>

### Other anogenital cancers

High-risk HPV types (predominantly types 16 and 18) are also implicated in 50 to 90% of other anogenital cancers in both women and men, including cancers of the vulva, vagina, anus, and penis, although these types have almost no role in

causing non-malignant lesions (see below). In Australia in 2001, there were 252 vulvar cancers (2.6 per 100 000), 62 vaginal cancers (0.6 per 100 000) and 225 anal cancers (1.2 per 100 000) diagnosed.<sup>40</sup>

### Non-malignant lesions

Genital warts are a common manifestation of HPV type 6 and 11 infection. Genital warts can cause significant psychological morbidity. In Australia, 4.0% of men and 4.4% of women aged 16–59 years report ever being diagnosed with genital warts.<sup>41</sup> These prevalence estimates translate into approximately 36 000 cases in Australia. The cumulative lifetime risk of genital warts has been estimated at 10%.<sup>42,43</sup> Peak attack rates occur in young women aged 15–24 years.<sup>44</sup> An analysis of data from the BEACH cross-sectional survey of national GP activity found that, between April 2000 and March 2003, consultations for genital warts in women aged 12–49 years occurred at a rate of 0.17 per 100 encounters.<sup>45</sup> Severe morbidity from genital warts, as measured by hospitalisation, is uncommon and peaks in women 20–24 years of age (26 per 100 000) (AIHW National Hospital Morbidity Database 2006). Morbidity not causing hospitalisation includes recurrence and a range of local complications. Worldwide, the best epidemiological data on genital wart incidence comes from the United Kingdom.<sup>2</sup>

Exposure to HPV types 6 and 11 at birth can also cause recurrent respiratory papillomatosis in children. This relatively rare disease, with an estimated incidence of 4 per 100 000 children,<sup>46,47</sup> is characterised by repeated growth of warts in the respiratory tract requiring repeated surgery. Adults can also develop recurrent respiratory papillomatosis.

### Type-specific HPV epidemiology

Worldwide, approximately 50% of cervical cancers contain HPV16 DNA and 16% contain HPV18 DNA.<sup>48,49</sup> Among cervical adenocarcinomas, 70% contain HPV 16 or 18 DNA, with HPV18 being relatively more common (37.7%) than HPV16 (31.3%).<sup>48</sup> HPV16 has been detected in 48% of HSILs, 19% of LSILs and 2% of cytologically normal women. HPV18 has been detected in 7% of HSILs, 6% of LSILs and 0.7% of cytologically normal women.<sup>50–52</sup> The low-risk HPV types 6 and 11 have been detected in 6.2% and 3.2% of LSILs respectively and each type in 0.1% of cytologically normal women.<sup>51,52</sup>

Australian studies indicate that the 5 most frequent HPV genotypes identified in 553 cervical cancers were HPV16 (60%), HPV18 (20%), HPV45 (5%), and HPV39 and HPV73 (2.3% each).<sup>53–57</sup> Best available Australian data indicate that HPV16 and HPV18 are, respectively, responsible for approximately 60%/20% of cervical cancers and 37%/8% of high-grade cervical abnormalities.<sup>53,54</sup>

## Vaccines

HPV vaccines have been developed using recombinant DNA technology based on virus-like particles (VLPs), which are not infectious and do not have any cancer-causing potential.

There are 2 HPV vaccines registered for use in Australia. The bivalent vaccine, 2vHPV vaccine (CERVARIX), contains VLPs of HPV genotypes 16 and 18, and is administered as a 3-dose schedule at 0, 1 and 6 months. The quadrivalent vaccine, 4vHPV vaccine (GARDASIL), is administered at 0, 2 and 6 months and contains VLPs of HPV genotypes 16, 18, 6 and 11.

- **CERVARIX** – GlaxoSmithKline (human papillomavirus vaccine – recombinant protein particulate (VLP) vaccine containing the major capsid (L1) protein of HPV types 16 and 18). Each 0.5 mL monodose pre-filled syringe or vial contains 20 µg each of HPV types 16 and 18 adjuvanted with AS04 (AS04 is comprised of 500 µg aluminium hydroxide and 50 µg of 3-O-desacyl-4'-monophosphoryl lipid A [MPL]); 4.4 mg sodium chloride; 624 µg sodium dihydrogen phosphate dihydrate.
- **GARDASIL** – CSL Biotherapies/Merck & Co Inc (human papillomavirus vaccine – recombinant protein particulate (VLP) vaccine containing the major capsid (L1) protein of HPV types 6, 11, 16 and 18). Each 0.5 mL monodose pre-filled syringe or vial contains 20, 40, 40 and 20 µg of HPV types 6, 11, 16 and 18, respectively, adsorbed onto 225 µg aluminium hydroxyphosphate sulphate; 9.65 mg of sodium chloride; 780 µg of L-histidine; 50 µg of polysorbate 80; 35 µg of sodium borate. May also contain yeast proteins.

It is important to note that HPV vaccines are prophylactic vaccines (ie. designed to prevent initial HPV infection). In women who are already infected with HPV types covered by the vaccines before vaccination (ie. HPV DNA positive), the vaccines do not treat infection or prevent disease caused by that type.<sup>58</sup>

In women HPV DNA negative and HPV seronegative for relevant types, both vaccines are highly effective at preventing persistent type-specific infection and related cervical disease (~90–100%).<sup>59–62</sup> The 4vHPV vaccine also has established efficacy against external genital lesions (warts, and vulval and vaginal dysplasias) in women. Vaccine efficacy against external genital lesions related to HPV 6, 11, 16 or 18 in women who were naïve to vaccine types at the beginning of the trials and who received 3 doses was 99% (95% CI: 95–100%).

Compared to HPV DNA negative and HPV seronegative women, vaccine efficacy (VE) in women who received vaccine regardless of HPV status at baseline and may, therefore, have had previous infection, was much lower. Against HPV16/18-related CIN2/3 or worse, VE was 44% (95% CI: 31–55%) at a mean of 3 years follow-up<sup>63</sup> and against high-grade CIN caused by any HPV type it

was 18% (95% CI: 7–29%).<sup>63</sup> However, vaccine efficacy is expected to be higher over a longer duration of follow-up, as the proportion of disease due to incident infection (where vaccination has an effect) increases compared to the proportion of disease due to infection/disease at baseline (which is not affected by the vaccine). These data reflect the reduced impact of vaccinating women in whom a proportion will already have been infected with HPV, eg. older women who are/ have been sexually active. Vaccine efficacy estimates in populations including women already infected with HPV at baseline have not yet been published for 2vHPV vaccine, but a similarly reduced impact, compared with an HPV naïve population, can be anticipated.

It is possible that HPV vaccines may provide some protective efficacy against disease due to types closely related to types 16 and 18, in particular HPV31 and HPV45, but published data supporting this hypothesis are currently limited to infection endpoints only and are imprecise.<sup>60,64-66</sup>

When given as a 3-dose series, HPV vaccines elicit neutralising antibody titres many times higher than those observed following natural infection.<sup>67-69</sup> Antibody responses peak at month 7 (1 month after dose 3) at titres between 7 and 150 times greater than following natural infection, depending upon the HPV type and vaccine.<sup>59,62,70,71</sup> Following an initial decline, they appear to plateau at 18 to 24 months, remaining stable for at least 5 years at levels above or at least equivalent to those seen following natural infection.<sup>58,60,62,70</sup> It should be noted that there is no standard serological assay for detecting HPV antibodies and no protective titre has been established. Therefore, absolute titres achieved (as reported in the randomised trials) are not directly comparable between 2vHPV and 4vHPV vaccines. Similarly, differences in methodologies and the populations examined make direct comparisons of published 4vHPV and 2vHPV vaccine efficacy estimates difficult.

Overall, seroconversion occurs in 99 to 100% of those vaccinated.<sup>58,60,61</sup> The duration of immunity after vaccination is not yet known (but is of at least 5 years' duration); hence, it is possible that booster doses may be required in the future.<sup>58,60,62</sup>

There are currently no clinical efficacy data available in males or in pre-adolescent females (as collection of genital specimens is not appropriate). Antibody response to both 4vHPV and 2vHPV vaccination has been evaluated in pre-adolescent and adolescent females (9–15 years of age and 10–14 years of age, respectively). In males, antibody response has only been studied for 4vHPV, and only in the age group 9–15 years, through immunological bridging studies.<sup>72,73</sup> Young males and females administered 4vHPV vaccine and females aged 10–14 years administered 2vHPV vaccine produce antibody responses that are at least 2-fold higher compared to women in whom clinical efficacy has been demonstrated. The peak antibody levels achieved following vaccination decrease with age. Immunobridging studies for older women (aged >26 – ≤45 years) administered the 2vHPV demonstrate antibody titres in a comparable range to women in the 15–25 year age group who are in the plateau phase of long-term follow-up.

These data were current at the time of publishing *The Australian Immunisation Handbook*.

## Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.<sup>74</sup> Store at +2°C to +8°C. Do not freeze. Protect from light.

## Dosage and administration

The dose of 2vHPV vaccine is 0.5 mL administered by IM injection. The recommended schedule is 0, 1 and 6 months. The second dose of 2vHPV can be administered between 1 and 2.5 months after the first dose.

The dose of 4vHPV vaccine is 0.5 mL administered by IM injection. The recommended schedule is 0, 2 and 6 months. In clinical studies, efficacy for 4vHPV vaccine has been demonstrated in individuals who have received all 3 doses within a 1 year period. Where flexibility in the recommended dosing schedule is unavoidable, the second dose should be administered at least 1 month after the first dose and the third dose should be administered at least 3 months after the second. There is no need to repeat earlier doses. Give missing dose(s) as soon as is practicable, making efforts to complete doses within 12 months.

4vHPV vaccine has been administered concomitantly with hepatitis B vaccine in clinical trials, with no reduction in immunogenicity of either vaccine observed.

There are no clinical data regarding concomitant administration of either 2vHPV or 4vHPV vaccine with adolescent/adult formulation dTpa or varicella vaccine, but there is no reason to expect any adverse outcomes if they are given simultaneously, using different injection sites.

## Recommendations

Both vaccines are recommended to provide protection against oncogenic HPV type 16 and/or 18 cervical disease. If protection against genital warts is desired, the 4vHPV vaccine provides protection against HPV types 6 and 11, which are associated with more than 90% of these lesions.<sup>67</sup> (See also 'Vaccines' above.)

(i) Females aged 10–13 years (*Safety-Grade B*)(*Efficacy-no data*)(*Immunogenicity-Grade B*)<sup>67</sup>

HPV vaccine is recommended for females 10–13 years of age. Currently only the 4vHPV vaccine is on the NIP schedule for females aged 12–13 years. Please refer to your State/Territory health authority for further information (see Appendix 1, *Contact details for Australian, State and Territory Government health authorities and communicable disease control*).

(ii) Females aged 14–18 years (*Safety-Grade B*)(*Efficacy-Grade B*)(*Immunogenicity-Grade B*)<sup>67</sup>

HPV vaccine is also recommended for females 14–18 years of age. While some females in this age group will already have commenced sexual activity, the majority will not yet be infected with a HPV vaccine type.

(iii) Females aged 19–26 years (*Safety-Grade A*)(*Efficacy-Grade A*)(*Immunogenicity-Grade A*)<sup>67</sup>

HPV vaccine is also recommended for females 19–26 years of age.

In females in this age group who have never had sexual intercourse the vaccine efficacy will be comparable to younger women, and HPV vaccination is recommended. In sexually active females 19–26 years of age, the overall benefit from HPV vaccination is likely to be less; however, past or current infection with all HPV types covered by the vaccine is unlikely.

NB. The absolute benefit of HPV vaccine to an individual sexually active woman cannot be determined clinically, as appropriate tests to detect both previous and current HPV infection with vaccine types are not available.

In all sexually active women, the most important preventive intervention against cervical disease remains regular Pap screening. Vaccination is not an alternative to Pap screening but is complementary. The National Cervical Screening Program recommends routine screening with Pap smears every 2 years for all women between the ages of 18 (or 2 years after first sexual intercourse, if later) and 69 years.

(iv) Females aged  $\geq 27$  years (*Safety 2vHPV vaccine-Grade B; 4vHPV vaccine-no data*)(*Efficacy-no data*)(*Immunogenicity 2vHPV-Grade B; 4vHPV-no data*)<sup>67</sup>

2vHPV vaccine is registered for use in females 27– $\leq 45$  years of age on the basis of safety and bridging immunogenicity data. The extent of benefit that can be expected to be derived from the use of HPV vaccine in this age group will depend upon past sexual history and the likelihood of new sexual partners in the future (ie. an assessment of likely past and future HPV exposure) and the sexual behaviour of her male partner(s). HPV-related cervical infection and Pap test abnormalities peak in women aged  $<30$  years in Australia.

4vHPV vaccine is not registered for use in females over the age of 27 years as there are no safety or efficacy data to support its use in this age group.

In all sexually active women, the most important preventive intervention against cervical disease remains regular Pap screening. Vaccination is not an alternative to Pap screening but is complementary. The National Cervical Screening Program recommends routine screening with Pap smears every 2 years for all women between the ages of 18 (or 2 years after first sexual intercourse, if later) and 69 years.

For women who have recently been diagnosed with cervical dysplasia, or have been treated for this in the past, HPV vaccine will have no impact on current disease, but may prevent future dysplasia due to a different HPV vaccine type.

(v) Males [For males aged 9–15 years (*Safety 4 vHPV vaccine-Grade B; 2vHPV vaccine-no data*)(*Efficacy-no data*)(*Immunogenicity 4vHPV vaccine-Grade B; 2vHPV vaccine-no data*)]<sup>67</sup>

4vHPV vaccine is licensed for use in males aged 9–15 years. 4vHPV vaccine produces high antibody titres in pre-adolescent and adolescent males but it is not known whether vaccination of males can either prevent transmission of HPV or provide protection against genital HPV infection, genital warts, anogenital dysplasia or anogenital cancers. 2vHPV vaccine is not registered for use in males. There is no recommendation for vaccination of males at this time due to the lack of clinical efficacy data.

## Contraindications

The only absolute contraindications to HPV vaccine are:

- anaphylaxis following a previous dose of the vaccine, or
- anaphylaxis to any vaccine component. The 4vHPV vaccine may contain minute amounts of yeast proteins.

## Precautions

### People with impaired immunity

There are limited clinical trial data available for this group. However, as HPV vaccines are not live vaccines, they can be administered to women who are immunosuppressed as a result of disease or medications. The immune response and vaccine efficacy might be less than in individuals who are immunocompetent (see Chapter 2.3, Subsection 2.3.3, *Vaccination of individuals with impaired immunity due to disease or treatment*).

## Adverse events

Both the 2vHPV and 4vHPV vaccines are generally safe and well tolerated. A variety of comparators were used in clinical trials of 2vHPV and 4vHPV, but data comparing vaccine adverse events with an aluminium-containing placebo are available for both vaccines and are quoted below for common local adverse reactions. More detailed information about adverse events occurring in the vaccine trials is available from the product information for 2vHPV vaccine and from the US FDA for 4vHPV.<sup>75</sup>

In clinical trials of the 2vHPV vaccine, the most commonly reported adverse events were injection site pain 78%, swelling ~26% and erythema ~30% compared to ~53%, ~8% and 11% in the aluminium hydroxide placebo group. Incidence of injection site pain decreased across the 3 doses, whereas there was

a slight increase in the reported proportion with swelling and erythema after successive doses.

In clinical trials of the 4vHPV vaccine the most commonly reported adverse events were injection site pain ~81%, swelling ~24% and erythema ~24%, compared to ~75%, ~16% and ~18% in the aluminium-containing placebo group. The incidence of injection site pain was approximately equal across the 3 doses, whereas there was a modest increase in the reported proportion with swelling and erythema after successive doses.

HPV vaccines are well tolerated by those who have already been exposed to the HPV types included in the vaccine.

### **Use in pregnancy**

HPV vaccine should not be given during pregnancy (see Chapter 2.3, Subsection 2.3.2, *Vaccination of women planning pregnancy, pregnant or breastfeeding women, and preterm infants*).

It should be noted that there is no evidence from animal studies, or among HPV vaccine trial participants who inadvertently became pregnant, of teratogenicity or of adverse fetal outcomes and, therefore, HPV vaccination during pregnancy is not an indication for termination.

Where vaccine has inadvertently been administered during pregnancy, further doses should be deferred until after delivery.

### **Use during lactation**

HPV vaccine may be given while lactating (see Chapter 2.3, Subsection 2.3.2, *Vaccination of women planning pregnancy, pregnant or breastfeeding women, and preterm infants*).

In trials, 995 nursing mothers received 4vHPV vaccine or placebo, and no relation between vaccination and adverse events was observed. The effect on breastfed infants of the administration of 2vHPV vaccine to their mothers has not been evaluated in clinical studies. It is not known whether HPV vaccine antigens or HPV antibodies are excreted in human milk.

### **Variations from product information**

None.

### **References**

Full reference list available on the electronic *Handbook* or website <http://immunise.health.gov.au>.