4.6 HUMAN PAPILLOMAVIRUS

4.6.1 Virology

Human papillomaviruses (HPVs) are small, non-enveloped viruses with circular double-stranded DNA. HPVs infect and replicate primarily within cutaneous and mucosal epithelial tissues.

More than 100 HPV genotypes have been identified based on sequence variations in the major genes. They differ in their preferred site of infection; approximately 40 HPV types infect the anogenital tract. Some HPV types, including types 16, 18, 31, 33, 35, 45, 52 and 58, are designated as 'high-risk', as they are causally associated with the development of cancer. Other HPV types, including types 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81 and 89, have been classified as 'low-risk' and are predominantly associated with non-malignant lesions, such as genital warts. The other types are uncommon and their associations with disease are undetermined, but they are not currently believed to be significant causes of cancer.[1,2]

4.6.2 Clinical features

Transmission of anogenital HPV occurs primarily through sexual intercourse; however, virus transmission can less commonly occur following non-penetrative sexual contact.[3] Perinatal transmission of HPV can cause laryngeal infection in infants, rarely resulting in recurrent respiratory papillomatosis.[4] HPV infection is often subclinical, but, dependent upon the infecting HPV genotype, may result in lesions that include cutaneous warts, genital warts, respiratory papillomatosis (low-risk HPV types), and dysplasias and cancers of the cervix, vulva, vagina, penis, anus, and the oral cavity and oropharynx (high-risk HPV types). Most genital HPV infections are cleared (no longer detectable via HPV DNA testing) within 12 to 24 months. In about 3 to 10% of infections, the virus persists. Persons with persistent HPV infection constitute the at-risk group for development of HPV-associated cancers.[5-7]

The causal link between persistent cervical HPV infection and cervical cancer is well established. The strength of association between HPV infection and other cancers varies by site and oncogenic HPV type.[8]

Cellular changes that occur in the cervix as a result of HPV infection are referred to as cervical intraepithelial neoplasia (CIN). The majority of these changes regress, but a minority will progress to cervical cancer. Malignant transformation in the cervix usually occurs 10 to 20 years following infection with high-risk HPV types, but has been reported to occur in less than 2 years.[9]

The clinical features of other HPV-associated cancers and their precursor lesions in the anogenital region and oropharynx vary, and also depend on the anatomical site. The process of progression of HPV-associated precursor lesions to cancers in these sites is less well understood than the process in the cervix. Anogenital warts may present as painless lumps, or with local tenderness, itching or

bleeding. Recurrent respiratory papillomatosis is a potentially fatal condition that usually occurs in childhood, characterised by multiple warty excrescences on the mucosal surface of the respiratory tract.[10]

4.6.3 Epidemiology

Infection with HPV is very common in both men and women, with initial infection occurring close to the time of sexual debut. It is estimated that up to 79% of the general population will be infected with at least one genital type of HPV at some time in their lives.[11,12] A greater number of sexual partners is consistently found to be associated with an increased risk of HPV acquisition.[12] HPV infection rates differ between geographic regions, and estimated population prevalence of HPV also varies depending on the anatomical site and the lesions sampled. About two-thirds of Australian women aged 15–20 years participating in cervical screening had HPV DNA detected in cervical samples collected for cytology.[13]

Certain population subgroups are identified to be at increased risk of HPV infection and HPV-associated diseases, compared with the general population. Infection with multiple HPV genotypes and longer time to clear infection are commonly observed in men who have sex with men (MSM).[14-16] In addition, the prevalence of high-risk HPV types is significantly higher in HIV-positive MSM than in MSM who are HIV-negative.[14] Persons who are immunocompromised (due to disease or medical treatment) are at increased risk of HPV-related disease.[12]

In a serosurvey conducted in Australia in 2006, 24% of females and 18% of males aged 0–69 years were seropositive to at least one of the four HPV types 6, 11, 16 and 18[17] – noting that fewer than 60% of women, and an even lower proportion of men, who are infected with HPV develop antibodies.[18-20] The onset age of seropositivity for HPV in this study was 10–14 years in females and 15–19 years in males. The average age of sexual debut for both males and females in Australia was 16 years, as reported in 2000–2002.[21] A more recent national survey in 2008 reported that about 80% of senior secondary school children (aged approximately 15–19 years) acknowledged having engaged in some form of sexual activity that may transmit HPV.[22]

Persistent HPV infection is the necessary precursor for the development of all cervical cancers.[23] Worldwide, approximately 70% of cervical cancers contain HPV-16 DNA and 16% contain HPV-18 DNA.[24,25] Australian data indicate that HPV-16 and HPV-18 are responsible for approximately 60% and 20%, respectively, of cervical cancers, and 37% and 8%, respectively, of high-grade cervical abnormalities.[26,27] In Australia, cervical cancer ranked 22nd in the overall cancer disease burden in 2008 and now occurs predominantly in women unscreened or under-screened through the National Cervical Screening Program.[28,29] 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. The prevalence of high-risk HPV types 16 and 18, detected when cervical samples collected for cytology were tested for HPV DNA, was similar between Indigenous and non-Indigenous women.[13] However, the incidence rate of cervical cancer in Aboriginal and Torres Strait Islander women is almost 3 times higher than in non-Indigenous Australian women, an indication of lower participation rates in cervical screening programs by Indigenous Australians and greater prevalence of cofactors for cervical cancer such as smoking, earlier and more pregnancies, and lower socioeconomic status.[13,28,30] Indigenous women are 5 times more likely to die from cervical cancer than non-Indigenous women.[28] Also, Australians in remote and very remote areas have 1.5 times higher cervical cancer incidence than those living in major cities.[28]

The proportion of cancers of other anogenital sites that is attributable to HPV ranges from approximately 40% for vulval cancers to approximately 85% for anal cancers. More than 85% of these HPV-associated cancers have evidence of infection due to the high-risk HPV types 16 and 18.[31-36]

In Australia in 2007, incidence rates of vulval and vaginal cancers in women were 2.6 per 100 000 (n=276) and 0.65 per 100 000 (n=69), respectively.[28] The incidence rate of penile cancer was 0.8 per 100 000. The age-standardised incidence rate for anal cancer was 1.3 per 100 000; however, a slightly higher incidence was observed in females than in males. Overall, anal cancer incidence has been steadily increasing over the past few decades; however, the increase has been greater in males than in females.[31,34] The mortality rates for vulval, vaginal, penile and anal cancers were all less than 0.6 per 100 000.[28]

MSM have a significantly higher incidence of high-grade anal intraepithelial neoplasia and anal cancer than the general population. Overseas studies have found a greater than 30-fold higher incidence of anal cancer in MSM than in other men.[37,38]

There is wide variability in the reported proportions of oropharyngeal cancers associated with HPV, ranging from 12% to 63%, and a lower proportion of oral cancers.[39-41] Of the cancers at these sites that are HPV-positive, HPV-16 and/or HPV-18 account for more than 85%. In Australia, similar to the United States and other western countries, there has been a steady increase in the burden of HPV-positive oropharyngeal cancers (mainly attributable to cancers of the base of the tongue and tonsils) over the past few decades.[31,39,42-45]

The population incidence of benign HPV-associated lesions, such as anogenital warts, is much higher than the incidence of HPV-associated cancers. In Australia, the estimated annual incidence of anogenital warts in 2000–2006 was 206 per 100 000 in males and 231 per 100 000 in females. The age group of peak incidence was 25–29 years for men (rate 740 per 100 000) and 20–24 years for women (rate 861 per 100 000).[46] In Australia, 4.0% of men and 4.4% of women aged 16–59 years reported ever being diagnosed with genital warts,[47] and the estimated cumulative lifetime risk of genital warts was 10%.[48,49] The estimated incidence of

anogenital warts in MSM is about 10 times higher than in the general population, with a third of HIV-negative MSM reporting a history of these lesions.[46,50] HPV types 6 and 11 are associated with 90% of genital warts.[51,52]

Recurrent respiratory papillomatosis is a rare (incidence approximately 3.5 per 100 000) and predominantly childhood disease that is associated with HPV types 6 and 11 in 100% of cases.[52-54]

In 2007, the HPV Vaccination Program, funded under the NIP, was introduced. This initially included universal vaccination of girls aged approximately 12–13 years, delivered through an ongoing school-based program. It also included a catch-up program for females up to 26 years of age, which ceased at the end of 2009. In 2013, the program will be extended to include HPV vaccine for boys aged approximately 12–13 years, together with a 2-year catch-up program for Year 9 boys. Although the impact of HPV vaccination on cancer incidence will take decades to occur, early surveillance data have shown an impact on the incidence of genital warts and CIN in the years following the introduction of the female vaccination program.[55-58] A study including eight sexual health centres showed a 59% decrease in the proportion of vaccine-eligible female first-time clinic attendees diagnosed with genital warts.[56] This study also demonstrated that vaccination of females results in some herd immunity benefits to males, with a significant decline in the diagnosis of genital warts observed in unvaccinated males of the same age.[55,56,58] In addition to reduction in genital warts, Victorian data have demonstrated a 48% decline in the incidence of high-grade cervical abnormalities in girls aged <18 years in the years after the introduction of the HPV Vaccination Program.[57] National cervical screening data are also indicating a decline in high-grade lesions diagnosed in women aged <20 years.[29]

4.6.4 Vaccines

There are two HPV vaccines registered for use in Australia: the bivalent vaccine (2vHPV; Cervarix), which contains virus-like particles (VLPs) of HPV types 16 and 18; and the quadrivalent vaccine (4vHPV; Gardasil), which contains VLPs of HPV types 16, 18, 6 and 11. VLPs are not infectious and do not replicate or cause cellular abnormalities.[59,60]

- ***Cervarix*** – GlaxoSmithKline (recombinant protein particulate [VLP] vaccine containing the major capsid [L1] protein of HPV types 16 and 18; 2vHPV). Each 0.5 mL monodose vial or pre-filled syringe contains 20 μg HPV-16 L1 protein and 20 μg HPV-18 L1 protein, adjuvanted with AS04 (comprised of 0.5 mg aluminium hydroxide and 50 μg 3-O-desacyl-4′-monophosphoryl lipid A [MPL]).

- ***Gardasil*** – CSL Limited / Merck & Co Inc (recombinant protein particulate [VLP] vaccine containing the major capsid [L1] protein of HPV types 6, 11, 16 and 18; 4vHPV). Each 0.5 mL monodose vial or pre-filled syringe contains 20 μg HPV-6 L1 protein, 40 μg HPV-11 L1 protein, 40 μg HPV-16 L1 protein and 20 μg HPV-18 L1 protein, adsorbed onto 0.225 mg of aluminium as aluminium hydroxyphosphate sulphate; 0.780 mg L-histidine; 50 μg polysorbate 80; 35 μg sodium borate. May also contain yeast proteins.

The 2vHPV and 4vHPV vaccines have been assessed in females in a number of international clinical trials. When given as a 3-dose series, HPV vaccines elicit a neutralising antibody level many times higher than the level observed following natural infection.[61,62] Overall, seroconversion occurs in 97 to 100% of those vaccinated.[63-65] In women who are naïve to HPV types 16 and 18 prior to vaccination, both vaccines are highly effective at preventing type-specific persistent infection and related cervical disease (approximately 90 to 100%).[66-71] The 4vHPV vaccine also has established efficacy (100%; 95% CI: 94–100%) against external anogenital and vaginal lesions (genital warts, and vulval, vaginal, perineal and perianal dysplasias) associated with HPV types 6, 11, 16 or 18 in women.

In women who are vaccinated irrespective of their baseline HPV status (i.e. women who may have pre-existing HPV infection), vaccine efficacy is lower than observed in HPV-naïve women, indicating reduced vaccine effectiveness among women who are already sexually active. This is because both HPV vaccines are prophylactic vaccines (i.e. preventing primary HPV infection). Vaccination will not treat an existing HPV infection or prevent disease that may be caused by an existing HPV vaccine-type infection.[63,72,73] However, vaccination may still provide benefit for sexually active women by protecting them against new infections with other vaccine-preventable HPV types.

The efficacy of 4vHPV in males aged 16–26 years has been demonstrated in one clinical trial.[74] Vaccination was greater than 85% protective against persistent anogenital infection and external genital lesions due to vaccine HPV types among HPV-naïve participants. Among HPV-naïve MSM participants within the clinical trial, vaccine efficacy was 95% against intra-anal HPV infection and 75% against high-grade anal intraepithelial neoplasia from vaccine HPV types. Efficacy of 2vHPV vaccine in males has not been assessed to date; however, the vaccine has demonstrated safety and immunogenicity in males aged 10–18 years.[75]

There is some evidence of HPV vaccine providing some cross-protection to disease due to other HPV types in women: 4vHPV vaccine against cervical

disease due to HPV types 31 and 45[76] and 2vHPV vaccine against cervical disease due to HPV types 31, 33, 45 and 51.[77] However, the level of protection is less than for the vaccine HPV types and the durability of any such protection is unknown.

Efficacy of HPV vaccines in females or males <16 years of age was not assessed in pre-market trials due to the genital sampling requirements of such studies. However, the antibody responses observed in pre-adolescent and adolescent females and males (>9 years of age) were greater than those in adult women and men, in whom clinical efficacy has been demonstrated for both the 4vHPV and 2vHPV vaccines.

It is not certain how long immunity following HPV vaccination persists, or whether a booster dose after the primary course will ever be required. However, long-term population-based follow-up studies to assess this are underway.[78] In clinical trials, vaccine efficacy has been demonstrated up to at least 5 years for 4vHPV vaccine and 9.4 years for 2vHPV vaccine in women, with no breakthrough disease due to vaccine HPV types.[61,79,80]

Variations in vaccination schedules for both HPV vaccines are being assessed in clinical trials. A recent study showed a lesser immune response in a schedule with a dose interval of 12 months between each of the 3 doses of 4vHPV vaccine compared with schedules with dose intervals of 6 months or less between each of the doses.[81] However, a recent study of 2vHPV following an alternative schedule (0, 1 and 12 months) demonstrated that the immunogenicity of vaccine HPV types was non-inferior following this schedule, compared with the standard schedule (measured 1 month after the final dose).[82] Two-dose schedules of both 2vHPV and 4vHPV are also being studied.[83,84]

4.6.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[85] Store at +2°C to +8°C. Do not freeze. Protect from light.

4.6.6 Dosage and administration

The dose of both HPV vaccines is 0.5 mL to be given by IM injection.

The primary vaccination course for both HPV vaccines consists of 3 doses.

The recommended schedule for the 2vHPV vaccine is at times 0 (the day the 1st dose is given), 1 and 6 months. The 2vHPV vaccine is registered for use in females aged 10–45 years. The 2vHPV vaccine is not registered for use in males of any age.

The recommended schedule for the 4vHPV vaccine is at times 0 (the day the 1st dose is given), 2 and 6 months. The 4vHPV vaccine is registered for use in females aged 9–45 years and in males aged 9–26 years. However, there are no theoretical concerns that the efficacy or safety of 4vHPV vaccine in males up to the age of 45 years will differ significantly from females of the same age or younger males.

If scheduled doses have been missed, there is no need to repeat earlier doses. The missed dose(s) should be given as soon as is practicable, making efforts to complete doses within 12 months.

Where vaccines have been administered at less than the minimum intervals (see Table 2.1.12 *Catch-up schedule for persons ≥10 years of age (for vaccines recommended on a population level)*), contact your state or territory health department for guidance. See also Chief Medical Officer Guidance available at www.health.gov.au/internet/immunise/publishing.nsf/Content/cmo-full-advice-hpv-cnt.

Co-administration with other vaccines

Both HPV vaccines can be given concomitantly with reduced antigen content diphtheria-tetanus-acellular pertussis (dTpa) or diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine (dTpa-IPV), and hepatitis B vaccine (monovalent).[86-90] 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 of human papillomavirus vaccines

There are currently no clinical data available on the interchangeability of the two HPV vaccines. However, from first principles, acceptable antibody levels and protection against HPV-16 and 18 (the types that are shared by both these vaccines and that are the dominant causes of cervical cancer) would be expected following a combination schedule.

It is recommended that an HPV vaccination course commenced with one vaccine should, wherever possible, be completed with that vaccine and according to its recommended schedule.

Where the course includes a combination of the two HPV vaccines, either inadvertently or because of an adverse event following one vaccine, the person is considered to be fully immunised against HPV-16 and 18 disease if a total of 3 doses of HPV vaccine have been given, provided that the minimum interval requirements between the doses are satisfied. Every effort should be made to complete a 3-dose schedule for effective protection against disease due to each of the vaccine HPV types.

4.6.7 Recommendations

Neither HPV vaccine is registered or recommended for use in children <9 years of age.

Females

Both the 4vHPV and 2vHPV vaccines are recommended for use in females for prevention of persistent infection and anogenital disease caused by HPV types 16 and 18. The 4vHPV vaccine also provides protection against vaccine-type genital warts (which are mostly caused by HPV types 6 and 11). (See also 4.6.4 *Vaccines* above.)

Children and adolescents aged 9–18 years

HPV vaccine is recommended for females 9–18 years of age. The optimal age for administering the HPV vaccine is approximately 11–13 years, as most females in this age group would not have commenced sexual activity and so would be naïve to all HPV types. Vaccination only provides protection against vaccine-type disease if the vaccine is delivered prior to acquisition of that HPV type. Therefore, the decision to vaccinate older adolescent females, who may have already commenced sexual activities, should follow an assessment of the potential benefits, based on their likely previous HPV exposure and future risks of HPV exposure.

Either of the HPV vaccines can be used for adolescent females. The 2vHPV vaccine is only registered for use in girls ≥10 years of age.

Adults aged ≥19 years

Vaccination of all women in this age group is not routinely recommended, as many are likely to have been exposed to one or more vaccine HPV types through sexual activity (see 4.6.3 *Epidemiology* above).

However, some adult females may gain an individual benefit from HPV vaccination. The decision to vaccinate older females should take into account their likelihood of previous exposure to HPV and their future risks of HPV exposure.

Males

The 4vHPV vaccine is recommended for use in males for prevention of persistent infection and anogenital disease caused by HPV types 6, 11, 16 and 18. The 4vHPV vaccine also provides protection against vaccine-type genital warts (which are mostly caused by HPV types 6 and 11). (See also 4.6.4 *Vaccines* above.)

Children and adolescents aged 9–18 years

The 4vHPV vaccine is recommended for males 9–18 years of age. The optimal age for administering the 4vHPV vaccine is approximately 11–13 years, as most males in this age group would not have commenced sexual activity and so would be naïve to all HPV types. Vaccination only provides protection against vaccine-type disease if the vaccine is delivered prior to acquisition of that HPV type. Therefore, the decision to vaccinate older adolescent males, who may have already commenced sexual activities, should follow an assessment of the potential benefits, based on their likely previous HPV exposure and future risks of HPV exposure.

Adults aged ≥19 years

Vaccination of all men in this age group is not routinely recommended as many are likely to have been exposed to one or more vaccine HPV types through sexual activity (see 4.6.3 *Epidemiology* above).

However, some adult males may gain an individual benefit from HPV vaccination. The decision to vaccinate older males should take into account their likelihood of previous exposure to HPV and their future risks of HPV exposure.

Men who have sex with men

The 4vHPV vaccine is recommended for men who have sex with men (MSM) who have not previously been vaccinated with 3 doses of HPV vaccine. The decision to vaccinate males in this group should take into account their likelihood of previous exposure to HPV and their future risks of HPV exposure. Overall, MSM are at increased risk of persistent HPV infection and associated disease (independent of HIV status or the presence of other immunocompromising conditions).[14,38] In addition, at the population level, MSM are less likely to benefit from herd immunity attained from HPV vaccination of females. The safety and efficacy of 4vHPV vaccine has been demonstrated in MSM participants in a randomised clinical trial (see 4.6.4 *Vaccines* above).

Persons who are immunocompromised

HPV vaccine is recommended for adult men and women who are immunocompromised due to medical conditions (including HIV infection) or treatment. 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 (see 3.3.3 *Vaccination of immunocompromised persons*). Immunocompromised adolescents who have not yet been vaccinated with 3 doses of HPV vaccine should be offered catch-up vaccination. This is based on evidence that persons who are immunocompromised are more likely to develop a persistent HPV infection and to subsequently progress to HPV-related disease.[14,91]

There are currently no clinical trial data demonstrating the efficacy of either of the HPV vaccines in immunocompromised participants. However, 4vHPV has been shown to be well tolerated and immunogenic in HIV-infected males and women with systemic lupus erythematosus.[92-94] As HPV vaccines are not live viral vaccines, there are no specific safety concerns regarding administration to immunocompromised persons (see 3.3.3 *Vaccination of immunocompromised persons*).

Cervical screening in vaccinated females

For all sexually active women, regular cervical screening remains an important preventive measure against cervical disease (refer to the National Cervical Screening Program at www.cancerscreening.gov.au). Vaccination is not an alternative to cervical screening but is a complementary preventive measure, as HPV types other than those included in the current vaccines have the potential to cause cervical cancer. Likewise cervical screening is not an alternative to HPV vaccination. Both are recommended.

Cervical screening detects histopathological changes. It is not recommended to test for the presence of HPV virus or antibody routinely as a way of determining whether HPV vaccination is indicated.

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 different HPV types included in the vaccine.

4.6.8 Pregnancy and breastfeeding

HPV vaccines are not recommended for pregnant women.

Women who become pregnant after starting the HPV vaccination course should withhold getting further doses of the HPV vaccine while pregnant, and receive the remaining doses of the course after pregnancy.

Females who inadvertently receive a dose of HPV vaccine around the time of conception or during pregnancy should be informed of the body of evidence supporting lack of harm from vaccine administration in this setting. Among women who became pregnant during the course of 4vHPV vaccine clinical trials (despite recommendations for participants to avoid pregnancy), the overall proportions of pregnancies that resulted in an adverse outcome (spontaneous abortion, late fetal death, infant with congenital anomalies) were similar among 4vHPV vaccine recipients and placebo or control vaccine recipients. Although one clinical trial raised the possibility of an association between 4vHPV vaccine administered within 30 days following the estimated date of conception and an increased incidence of congenital anomalies in the infant, those conditions were relatively common and unrelated.[72] Pooled analyses from multiple clinical trials have not confirmed such an association.[95]

Pooled analysis of women who became pregnant during clinical trials showed that, overall, there were no differences in pregnancy outcomes between 2vHPV vaccine and control vaccine recipients.[96,97]

HPV vaccines can be given to breastfeeding women. Among breastfeeding mothers in the clinical studies of 4vHPV vaccine, the rates of adverse events in the mother and the breastfeeding infant were comparable between 4vHPV vaccine and control vaccination groups.[98] The effect on breastfed infants of the administration of 2vHPV vaccine to their mothers has not been evaluated directly in clinical studies, but breastfeeding is not considered a contraindication for receiving the 2vHPV vaccine.

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.6.9 Contraindications

The only absolute contraindications to HPV vaccines are:

- anaphylaxis following a previous dose of either HPV vaccine
- anaphylaxis following any vaccine component.

In particular, the 4vHPV vaccine is contraindicated in persons with a history of anaphylaxis to yeast.

4.6.10 Adverse events

Both the 2vHPV and 4vHPV vaccines are generally safe and well tolerated.

For both vaccines, injection site pain was the most commonly reported adverse event (approximately 80% of recipients), followed by swelling and erythema (20–30% for each). Injection site reactions were more commonly reported in vaccine recipients than in recipients of aluminium-containing placebo or control vaccines in clinical trials. Systemic reactions were also very common following both vaccines, occurring in up to about 30% of recipients. The most common adverse events included headache, fatigue, fever and myalgia. In most of the clinical trials, the frequencies of most of these common systemic adverse events were comparable between the HPV vaccine and the control vaccine recipients. Meta-analyses on pooled data from multiple clinical trials on both the 2vHPV and 4vHPV vaccines have shown no increase in the risk of serious adverse events among vaccine recipients compared with control recipients.[99,100]

For both vaccines, the safety profile and the spectrum of adverse events following immunisation in males were similar to those reported in females of corresponding age groups,[74,75,101,102] although some of the studies were not direct comparison studies.

Post-marketing passive surveillance of HPV vaccine use in the United States has identified syncope (fainting) as one of the most common adverse events reported following 4vHPV vaccine in adolescent and young adult females.[103] A small proportion (about 10%) of syncopal episodes resulted in a fall with head injury.[103] Similar or higher rates of syncope have been reported in other countries, through different surveillance mechanisms.[104,105] However, a prospective adverse events surveillance study in the United States, based on over 600 000 records of vaccine doses administered, did not find any increased risk of syncope with 4vHPV vaccination compared to the expected rate following non-4vHPV vaccination in youths and adults.[106] Syncope (fainting) may follow any vaccination, especially in adolescents and young adults, but is preventable through appropriate precautions. (See also 2.3.2 *Adverse events following immunisation*). In an Australian study, 22 subjects (including 14 with syncope and 8 with syncopal seizure following 4vHPV vaccination) were reviewed in a Victorian clinic and received further doses while supine; no recurrence of syncope occurred.[104]

Anaphylaxis and other suspected hypersensitivity reactions, including skin rash, after 4vHPV vaccine have also been reported. The estimated incidence

rate of anaphylaxis following 4vHPV vaccine in Australia, as at June 2010, was 2.6 anaphylaxis episodes per million doses of vaccine distributed, which was within the rate range for other vaccines given to children and adolescents in international studies.[107] A prospective surveillance study in the United States did not find any increased risk of anaphylaxis or allergic reactions with 4vHPV vaccination compared to the expected rate following childhood vaccines.[106]

4.6.11 Variations from product information

The product information for the 4vHPV vaccine, Gardasil, states that this vaccine is indicated for use in males up to 26 years of age and females up to 45 years of age. The product information for the 2vHPV vaccine, Cervarix, states that this vaccine is indicated for use in females up to 45 years of age and is not registered for use in males of any age. The ATAGI instead recommends that some males aged >26 years, such as MSM and those who are immunocompromised, who are likely to derive an individual benefit from HPV vaccination, can be vaccinated with 4vHPV. The ATAGI also recommends that some females aged >45 years, such as those who are immunocompromised, can be vaccinated with either 2vHPV or 4vHPV, based on their individual risk of future HPV exposure and disease.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au