Human papillomavirus vaccination

Human papillomaviruses (HPVs) are common viruses. About 40 types often, and usually transiently, infect genital epithelia asymptomatically. Their importance lies in the causal relationship between persistent infection with some HPV types and the development of cancers of the cervix, anus, vagina, penis, vulva and oropharynx.

Prophylactic HPV vaccines have been developed which target the two most oncogenic of the high risk HPV types, types 16 and 18, which are responsible for about 70% of cervical cancer cases globally. Because these vaccines work by preventing initial HPV infection with targeted types, and have no therapeutic effect on current infection, they are best administered to young adolescents before initiation of sexual activity. Many countries now routinely administer HPV vaccination through either school-based programmes or through primary care services.

The hospital doctor may need to understand the vaccines in relation to situations where patients seek information because vaccine courses are incomplete, raise safety concerns about the vaccines, question how vaccinated women can have developed high grade cervical lesions requiring treatment, or enquire as to the suitability of the vaccine for use in immunosuppressed populations or in groups who are not covered by routinely funded programmes (according to their age or sex). This article provides an overview of the epidemiology of HPV, the safety and effectiveness of the HPV vaccines and information about their clinical use.

HPV infection and disease

Most sexually active people will be infected with genital type HPV during their lifetime. In females, prevalence peaks in the years following sexual debut, reflecting high rates of incident infection and lack of immunity, before plateauing, as summarized by Bosch et al (2008). As demonstrated by Giuliano et al (2011a), in males prevalence is more constant throughout life, suggesting that men are less likely to generate sterilizing immunity to the virus and may be more likely to have ongoing exposure. Most genital HPV infections are cleared within 6–12 months without symptoms, although HPV types 6 and 11 infections can cause genital warts.

If HPV infection with one of the 'high-risk' or oncogenic viruses (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and probably 68, as per Bouvard et al (2009)) persists, high-grade intraepithelial abnormalities may develop. If untreated over time (usually decades) these lesions may develop into cancer, although others will regress, as summarized by Schiffman et al (2007) (and as per *Figure 1*). This natural history forms the basis of cervical screening using Pap tests, which provides secondary prevention of cervical cancer by detecting and treating high-grade cervical intraepithelial neoplasia.

All squamous carcinomas and adenocarcinomas of the cervix are attributable to HPV. Each of the 40 genital HPV types may cause low-grade cervical abnormalities, which are indicative of acute HPV infection. HPV is also causally associated with around 88% of anal cancers, 70% of vaginal cancers, 43% of vulvar cancers, 50% of penile cancers and 30% of oropharyngeal cancers, although attributable fractions may vary across populations dependent upon the presence of competing causes, as reported by Forman et al (2012).

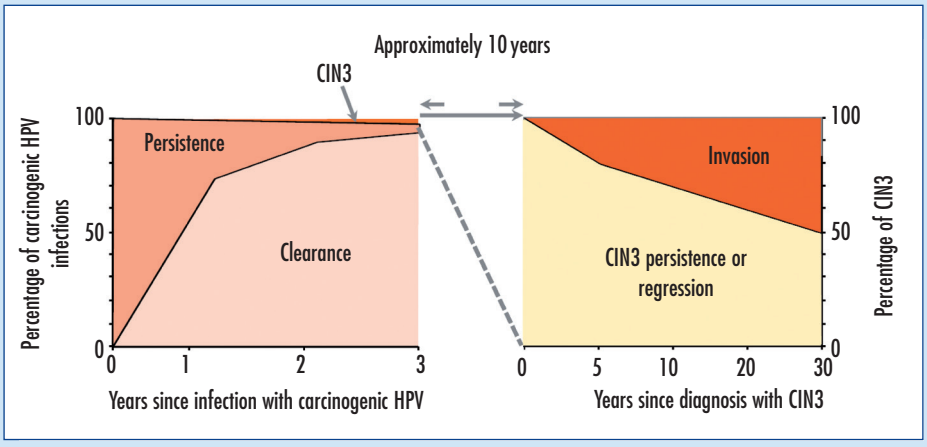
Other HPV-related cancers occur at lower rates in the general population than cervical cancers (2 per 100 000 per year or less), with or without cervical screening programmes, although in some populations anal cancers and HPV-related oropharyngeal cancer rates appear to be increasing, probably as a result of changes in sexual behaviour. No screening programmes are currently available for non-cervical HPV-related cancers.

How do HPV vaccines work

The two prophylactic HPV vaccines currently in use (a quadrivalent vaccine, Gardasil and a bivalent vaccine, Cervarix) both generate high levels of antibody against types 16 and 18, the two most oncogenic HPV types. As Day et al (2010) have reported, these antibodies block a conformational change that the virus needs to make in order to enter and infect the basal epithelial cell. As the virus can only access the basal epithelium at sites of minor trauma, exposure to antibodies in sera occurs at these sites.

As described by Bosch et al (2008), HPV16 and 18 are detected in 70% of cervical cancers and in 50% of high-grade

Figure 1. Natural history of human papillomavirus (HPV) infection. CIN3 = cervical intraepithelial neoplasia 3. Adapted from Moscicki et al (2012).



Dr Julia ML Brotherton *is Medical Director of the National HPV Vaccination Program Register, Victorian Cytology Service, East Melbourne, Victoria 8002, Australia and Honorary Senior Fellow, School of Global and Population Health, University of Melbourne, Victoria, Australia (jbrother@vcs.org.au)*

cervical lesions (other high risk types may also cause these lesions but HPV16/18-related lesions are more likely to progress). However, they are only found in about 35% of low-grade lesions, as all 40 HPV types may cause these, as reported by Clifford et al (2005).

As described by Schiller et al (2012), the vaccines are made using recombinant technology which produces the L1 outer coat protein of the virus, which self-assembles into virus-like particles which resemble the surface structure of the actual virus. These particles are not infectious or oncogenic as they contain no viral DNA. They generate high levels of antibody many times greater than seen following natural infection, particularly in combination with the adjuvants present in the vaccines. Gardasil also contains particles based on the L1 proteins of HPV6 and 11, which are the HPV types responsible for over 90% of genital warts and for recurrent respiratory papillomatosis. *Table 1* summarizes characteristics of the two vaccines.

Vaccine efficacy

Schiller et al (2012) have summarized the results of the large scale randomized controlled trials which established that both vaccines have very high efficacy against high-grade cervical intraepithelial neoplasia caused by HPV16 and 18, when given to women who were uninfected at baseline. They also effectively prevent infection, low-grade lesions, vulval and/or vaginal intraepithelial lesions and, for the quadrivalent vaccine, genital warts. A trial of the quadrivalent vaccine in males has also demonstrated protection against type-specific infection, external genital lesions (predominantly genital warts) and anal intraepithelial lesions, assessed among men who have sex with men, as reported by Palefsky et al (2011) and Giuliano et al (2011b). The trials indicated that the vaccines do not effectively treat infections or lesions already present before vaccination.

Currently duration of efficacy among trial participants is around 10 years, with ongoing monitoring being undertaken. As estimated in mathematical modelling by David et al (2009), the rate of decay of antibody titres suggests that protection will be long term.

Cross protection

Post-hoc analyses of the trials demonstrated that the vaccines offer some cross-protection against non-targeted but related HPV types. The bivalent vaccine (which produces higher antibody titres as a result of its adjuvant system) has considerable and significant protection against types 31 and 45 (>75%) and significant although lesser protection against types 33, 51 and 52. The quadrivalent vaccine provides significant protection against infection with type 31 (46%) (as summarized by Schiller et al (2012)). However, reported levels of antibody against related types are many fold lower than against targeted types and their duration is uncertain. Howell-Jones et al (2013) documented slight declines in genital warts in the UK following population-based vaccination with the bivalent vaccine, indicating that low levels of cross protection against HPV types 6 and 11 may be induced by that vaccine.

Vaccine impact

Vaccine impact is being monitored in HPV vaccinated populations around the world. Surveillance studies to date have noted substantial declines in HPV infection, genital warts and cervical disease in vaccine targeted cohorts. Declines in HPV infection are restricted to vaccine-targeted types in populations vaccinated with the quadrivalent vaccine, but Kavanagh et al (2014) noted declines in HPV types 31, 33 and 45 in Scotland following bivalent vaccination.

As Ali et al (2013) reported, genital warts have declined substantially in Australia, even among men of the same age as vaccinated women, indicating herd immunity. Vaccine effectiveness against high-grade cervical lesions in Australia of around 45% has been observed by Gertig et al (2013) and Crowe et al (2014), consistent with the expected impact on these lesions given that not all are caused by HPV16/18. As discussed by Heley and Brotherton (2009), high-grade abnormalities will continue to occur in vaccinated women and are not a cause for alarm, given that other HPV types can also cause these lesions and some women, particularly in catch-up vaccination programmes, were sexually active (HPV-exposed) before vaccination.

Table 1. Characteristics of prophylactic human papillomavirus (HPV) vaccines

	Quadrivalent HPV vaccine	Bivalent HPV vaccine
Brand name, manufacturer	Gardasil/Silgard, Merck & Co	Cervarix, GlaxoSmith Kline
Year and country first registered	June 2006 in USA	May 2007 in Australia
L1 virus-like particles	HPV types 6, 11, 16, 18	HPV types 16, 18
Number of doses distributed	>161 million (to end June 2014)	>49 million (to end May 2014)
Expression system for L1 protein	*Saccharomyces cerevesiae* (Baker's yeast)	*Trichoplusia ni* insect cells infected with L1 recombinant baculovirus
Adjuvant system	Aluminium hydroxyphosphate sulfate	Aluminium hydroxide and 3-O-deacytlated-4'-monophoshoryl lipid A (a detoxified bacterial lipopolysaccharide)
Percentage experiencing injection site reactions*	Any pain 72% (95% CI 68–75%) Any redness 26% (95% CI 22–30%) Any swelling 22% (95% CI 18–26%)	Any pain 93% (95% CI 90–95%) Any redness 44% (95% CI 40–49%) Any swelling 37% (95% CI 32–41%)
Standard three dose schedule	0, 2, 6 months	0, 1, 6 months

CI = confidence interval. * From Einstein et al (2009)

Vaccine safety

As summarized by Macartney et al (2013), post-vaccination safety surveillance studies have confirmed the findings of the clinical trials that the most common adverse events experienced following HPV vaccination are injection site reactions and minor systemic symptoms such as headache and dizziness. Local reactions of pain, redness and swelling at the injection site occur more frequently with the bivalent vaccine than the quadrivalent vaccine (*Table 1*). As at mid 2014, over 210 million doses of the vaccines have been distributed globally (over 161 million dose of quadrivalent vaccine and over 49 million doses of bivalent vaccine).

In response to case reports, systematic population-based studies, such as that of Arnheim-Dahlstrom et al (2013), have been undertaken. These have found no evidence of any association between the occurrence of autoimmune, neurological or thomboembolic events and HPV. Cases of anaphylaxis may rarely occur following HPV vaccination, as with other vaccines. No adverse effects have been noted after inadvertent administration during pregnancy, but the vaccines should not be given in pregnancy for precautionary reasons.

Clinical use of the vaccines

Many countries have now implemented government-funded HPV vaccination programmes, usually targeting pre-adolescent females given that maximum effectiveness of the vaccines is achieved when vaccination is given before HPV exposure. The choice of vaccine and age of the target population may be determined by local health priorities and cost-effectiveness analyses, which incorporate knowledge about local health-care costs, vaccine delivery systems and population demographics such as median age of sexual debut.

Vaccine schedules and administration

Both vaccines were administered in the initial trials and registered using a three-dose schedule with doses given over 6 months (at time points 0, 1–2 months and 6 months)(*Table 1*). In 2014, the World Health Organization (2014) and the European Medicines Agency also approved the use of two-dose HPV vaccine schedules for both HPV vaccines. This schedule can only be used for those aged 14 years or younger at the age of first dose. The two doses must be given 6 months or more apart, with an absolute minimum interval of 5 months (ensuring this is a prime-boost strategy).

This endorsement is based on demonstration of equivalent antibody responses against targeted HPV types in pre-adolescent females as those demonstrated following three doses administered to older females in whom vaccine efficacy has been demonstrated (Dobson et al, 2013; Romanowski et al, 2014). Some countries are adopting two-dose schedules for routine vaccination of young adolescents. The first two doses of the three-dose schedule (given 1–2 months apart) should not be considered adequate protection and those vaccinated according to this schedule require the third dose.

If a dose is missed, it can be administered without needing to restart the vaccination course. HPV vaccination courses should never be restarted. Doses spaced more widely apart than recommended will still result in adequate immunity, whereas doses administered closer than recommended may compromise the adequacy of protection. Local guidelines regarding the need for further doses in such situations (i.e. a fourth dose) should be followed (e.g. UK Green Book).

As Noronha et al (2014) have shown, HPV vaccines can be safely co-administered with other routinely scheduled vaccines without compromising immune responses to the vaccines. If an individual is given a course of vaccine containing both the vaccines (i.e. two doses of one and one of another), they should be advised that protection against genital warts may be less complete than if they had received three doses of quadrivalent vaccine.

Elective HPV vaccination

Outside of government-funded HPV vaccination programmes, individuals may choose to receive HPV vaccination at their own expense. Groups at particular risk from HPV, such as men who have sex with men (who are at a higher risk of genital warts and anal cancer), HIV-positive people and other immunocompromised or immunosuppressed people (who are at higher risk of HPV-related malignancies), may wish to consider elective HPV vaccination. HPV vaccination is safe among immunocompromised populations (it is not a live vaccine) and produces adequate immune responses among HIV-infected populations (Weinberg et al, 2012). However, in a study by Kumar et al (2013), a poorer immune response to vaccination was noted among 47 transplant recipients. In countries where male vaccination is not funded, males may benefit from herd immunity as a result of female vaccination but individuals may wish to receive HPV vaccine in order to reduce their personal risk of genital warts, anogenital cancers and cancers of the oropharynx.

A post-hoc analysis of quadrivalent HPV vaccine trial data by Joura et al (2012), and a non-randomized study by Kang et al (2013), also suggest a benefit from vaccination in preventing recurrent disease among women treated for high-grade cervical intraepithelial neoplasia. This may be the result of prevention of re-infection from other sites of HPV infection in the genital tract or from sexual partners, among these women who are known to have a reduced ability to clear oncogenic HPV infection. Careful counselling is indicated when vaccinating post-treatment to ensure that the limitations of the vaccine when given in this situation are made clear (i.e. not a therapeutic vaccine and does not protect against all HPV types) to ensure ongoing follow up and screening occurs. **BJHM**

Figure 1 *is reproduced from Moscicki et al (2012) by kind permission of Elsevier.*

Conflict of interest: Dr JML Brotherton has been an investigator on investigator designed unrestricted epidemiological research grants partially funded through bioCSL/Merck but has received no personal financial benefits.

Ali H, Donovan B, Wand H, Read TR et al (2013) Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. *BMJ* **346**: f2032 (doi: 10.1136/bmj.f2032)

Arnheim-Dahlstrom L, Pasternak B, Svanstrom H, Sparen P, Hviid A (2013) Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. *BMJ* **347**: f5906 (doi: 10.1136/bmj.f5906)

Bosch FX, Burchell AN, Schiffman M et al (2008) Epidemiology and natural history of human papillomavirus infections and type-specific

implications in cervical neoplasia. *Vaccine* **26**(Suppl 10): K1–16 (doi: 10.1016/j.vaccine.2008.05.064)
Bouvard V, Baan R, Straif K et al (2009) A review of human carcinogens–Part B: biological agents. *Lancet Oncol* **10**: 321–2 (doi:10.1016/S1470-2045(09)70096-8)
Clifford GM, Rana RK, Franceschi S, Smith JS, Gough G, Pimenta JM (2005) Human papillomavirus genotype distribution in low-grade cervical lesions: comparison by geographic region and with cervical cancer. *Cancer Epidemiol Biomarkers Prev* **14**: 1157–64 (doi: 10.1158/1055-9965.EPI-04-0812)
Crowe E, Pandeya N, Brotherton JM et al (2014) Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities: case-control study nested within a population based screening programme in Australia. *BMJ* **348**: g1458 (doi: 10.1136/bmj.g1458)
David MP, Van Herck K, Hardt K et al (2009) Long-term persistence of anti-HPV-16 and -18 antibodies induced by vaccination with the AS04-adjuvanted cervical cancer vaccine: modeling of sustained antibody responses. *Gynecol Oncol* **115**: S1–6 (doi: 10.1016/j.ygyno.2009.01.011)
Day PM, Kines RC, Thompson CD et al (2010) In vivo mechanisms of vaccine-induced protection against HPV infection. *Cell Host Microbe* **8**: 260–70 (doi: 10.1016/j.chom.2010.08.003)
Dobson SR, McNeil S, Dionne M et al (2013) Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. *JAMA* **309**: 1793–802 (doi: 10.1001/jama.2013.1625)
Einstein MH, Baron M, Levin MJ et al (2009) From head to head vaccine comparison trial in women aged 18–26 years. *Hum Vaccin* **5**(10): 705–19 (doi: 10.4161/hv.5.10.9518)
Forman D, de Martel C, Lacey CJ et al (2012) Global burden of human papillomavirus and related diseases. *Vaccine* **30**(Suppl 5): F12–23 (doi: 10.1016/j.vaccine.2012.07.055)
Gertig DM, Brotherton JM, Budd AC, Drennan K, Chappell G, Saville AM (2013) Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study. *BMC Med* **11**: 227 (doi: 10.1186/1741-7015-11-227)
Giuliano AR, Lee JH, Fulp W et al (2011a) Incidence and clearance of genital human papillomavirus infection in men (HIM): a cohort study. *Lancet* **377**: 932–40 (doi: 10.1016/S0140-6736(10)62342-2)
Giuliano AR, Palefsky JM, Goldstone S et al (2011b) Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. *N Engl J Med* **364**: 401–11 (doi: 10.1056/NEJMoa0909537)
Heley S, Brotherton J (2009) Abnormal Pap tests after the HPV vaccine. *Aust Fam Physician* **38**: 977–9
Howell-Jones R, Soldan K, Wetten S et al (2013) Declining genital warts in young women in England associated with HPV 16/18 vaccination: an ecological study. *J Infect Dis* **208**: 1397–403 (doi: 10.1093/infdis/jit361)
Joura EA, Garland SM, Paavonen J et al (2012) Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data. *BMJ* **344**: e1401 (doi: 10.1136/bmj.e1401)
Kang WD, Choi HS, Kim SM (2013) Is vaccination with quadrivalent HPV vaccine after loop electrosurgical excision procedure effective in preventing recurrence in patients with high-grade cervical intraepithelial neoplasia (CIN2–3)? *Gynecol Oncol* **130**: 264–8 (doi: 10.1016/j.ygyno.2013.04.050)
Kavanagh K, Pollock KG, Potts A et al (2014) Introduction and sustained high coverage of the HPV bivalent vaccine leads to a reduction in prevalence of HPV 16/18 and closely related HPV types. *Br J Cancer* (doi: 10.1038/bjc.2014.198)
Kumar D, Unger ER, Panicker G, Medvedev P, Wilson L, Humar A (2013) Immunogenicity of quadrivalent human papillomavirus vaccine in organ transplant recipients. *Am J Transplant* **13**: 2411–17 (doi: 10.1111/ajt.12329)
Macartney KK, Chiu C, Georgousakis M, Brotherton JM (2013) Safety of Human Papillomavirus Vaccines: A Review. *Drug Saf* (doi: 10.1007/s40264-013-0039-5)
Moscicki AB, Schiffman M, Burchell A et al (2012) Updating the natural history of human papillomavirus and anogenital cancers. *Vaccine* **30S**: F24–33 (doi: 10.1016/j.vaccine.2012.05.089)
Noronha AS, Markowitz LE, Dunne EF (2014) Systematic review of human papillomavirus vaccine coadministration. *Vaccine* **32**(23): 2670–4 (doi: 10.1016/j.vaccine.2013.12.037)
Palefsky JM, Giuliano AR, Goldstone S et al (2011) HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *N Engl J Med* **365**: 1576–85 (doi: 10.1056/NEJMoa1010971)
Romanowski B, Schwarz TF, Ferguson LM et al (2014) Immune response to the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose or 3-dose schedule up to 4 years after vaccination: Results from a randomized study. *Hum Vaccin Immunother* **10**: 1155–65 (doi: 10.4161/hv.28022)
Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S (2007) Human papillomavirus and cervical cancer. *Lancet* **370**: 890–907 (doi:10.1016/S0140-6736(07)61416-0)
Schiller JT, Castellsague X, Garland SM (2012) A review of clinical trials of human papillomavirus prophylactic vaccines. *Vaccine* **30** (5): F123–38 (doi: 10.1016/j.vaccine.2012.04.108)
Weinberg A, Song LY, Saah A et al (2012) Humoral, mucosal, and cell-mediated immunity against vaccine and nonvaccine genotypes after administration of quadrivalent human papillomavirus vaccine to HIV-infected children. *J Infect Dis* **206**: 1309–18 (doi: 10.1093/infdis/jis489)
World Health Organization (2014) Meeting of the Strategic Advisory Group of Experts on immunization, April 2014 – conclusions and recommendations. *Wkly Epidemiol Rec* **89**(2): 221–36

KEY POINTS

- Two prophylactic human papillomavirus (HPV) vaccines are in use which prevent, but do not treat, HPV infection with the two most oncogenic of the high risk HPV types, types 16 and 18.
- Many countries now offer young/pre adolescents HPV vaccination as vaccination will be most effective at reducing HPV infection and disease in the population if administered before the onset of sexual activity.
- Studies have demonstrated falls in HPV infection, genital warts and high-grade cervical lesions in vaccinated populations.
- Vaccinated females still need to participate in cervical screening as the vaccines do not prevent infection with all high risk types. HPV16 and 18 are detected in about 50% of high-grade cervical lesions.
- The standard three-dose schedule is 0, 1, 6 months for the bivalent vaccine and 0, 2, 6 months for the quadrivalent vaccine.
- Recently licensed two-dose schedules (0, 6 months) should only be used in countries endorsing the use of this schedule in those <15 years of age.
- HPV vaccine courses never need to be restarted if interrupted. Vaccine doses may be ineffective if delivered at closer than recommended dose intervals. In such cases an additional dose may be warranted.
- HPV vaccines are very safe, with injection site reactions the commonest adverse reaction. They are not associated with an increased risk of autoimmune, neurological or thromboembolic events.
- Elective HPV vaccination may be considered, especially for those at increased risk of HPV-related diseases such as men who have sex with men, human immunodeficiency virus (HIV)-positive persons, immunosuppressed patients and women treated for high grade cervical disease.