HPV vaccination

By Dr Louise Farrell, Obstetrician & Gynaecologist

The TGA licensed Gardasil in Australia for females aged 9-26 and males aged 9-15 and in April this year, the Australian Government began free HPV vaccination for schoolgirls. In July, a PBS 'catch up' vaccination program for females up to the age of 26 will be available through GPs. HPV vaccines appear safe and effective in preventing disease associated with targeted HPV types. Beyond the current published five year follow-up, the duration of protection is unknown. However, booster vaccination at five years produces antibody levels far higher than after the initial course and because the vaccine was so effective in the trials, it is not known what threshold antibody levels are protective. Parents and young women have three concerns around vaccination: safety; effectiveness; and doctor recommendation. With 84% of mothers surveyed in Melbourne saying they would have their daughters vaccinated if their doctor recommended it, doctors need to be well informed.

HPV and cancer

HPV is associated with

- 99.7% of cervical cancers
- 50% of vulval, vaginal and penile cancers
- 85% of anal cancers
- 20% of oropharyngeal cancers
- 10% of cancers of larynx and aerodigestive tract
- Recurrent respiratory papillomatosis
- >90% of all genital warts

Of the 100 or so Papilloma strains that infect humans, more than 30 favour the female genital tract but only about half of these can cause cancer – the others are associated with epithelial proliferation.

Of the oncogenic strains, the most virulent HPV 16 and 18 account for 70% of all cervical cancers. Preventing infection by these two strains will substantially reduce the risk of cervical and other cancers (see table).

Table: Disease Coverage by HPV Type

HPV Type	Women	Men
16/18	• 70% of cervical cancer • 50% of CIN 2/3 • 25% of CIN 1 • Most anal cancers	• Most anal cancers • Prevention of infection (reduced transmission to women)
6/11	• 10% of CIN 1 • >90% of genital warts • Recurrent respiratory papillomatosis (RRP)	• Prevention of infection (reduced transmission to women) • >90% of genital warts • RRP

CIN = cervical intra-epithelial neoplasia; RRP = recurrent respiratory papillomatosis

HPV infection is very common in young females after sexual debut. Infection by any viral strain is usually transient, asymptomatic and resolves spontaneously. Factors associated with persistence are older age, infection with oncogenic types, and infection with multiple types.

As well as preventing most cancers in the lower genital tract of women, vaccination will reduce a significant number of abnormal Pap smears linked to HPV persistence. The burden of abnormal cytology falls largely on young women, with 80% of abnormal cytology in women aged <40. Because studies indicate possible adverse obstetric outcomes following excisional treatments for CIN, this makes it important to reduce these treatments in younger women.

HPV vaccines

Two vaccines have been developed: bivalent against types 16 and 18 (GSK Biological's *Cervarix,* awaiting licence in Australia); and quadrivalent vaccine against types 6, 11, 16 and 18 (Merck & Co's *Gardasil,* distributed by CSL).

Bivalent vaccine **Cervarix**	**Quadrivalent Vaccine** **Gardasil**
HPV16/18 L1 VLP	HPV 6/11/16/18 L1 VLP
Manufacture: insect-cell system via baculovirus	Manufacture: yeast system
20μg of HPV 16 & 20μg HPV 18 VLP in an adjuvant of 500μg aluminium hydroxide with 50μg of 3-deacylated monophosphoryl lipid A (ASO4)	20μg HPV 6, 40μg of HPV 11, 40μg HPV 16 & 20μg HPV 18 VLP in an adjuvant of 225μg aluminium hydroxy-phosphate sulfate (alum)
Given 3 doses IMI at 0, 1 & 6 months	Given 3 doses IMI at 0, 2 & 6 months

VLP = virus like particles

Vaccine safety

The vaccine is comprised of virus like particles (VLPs) that contain no genetic material, making them non-infectious and non-oncogenic. Both vaccines have been administered to large numbers of women in trials with very few serious side effects.

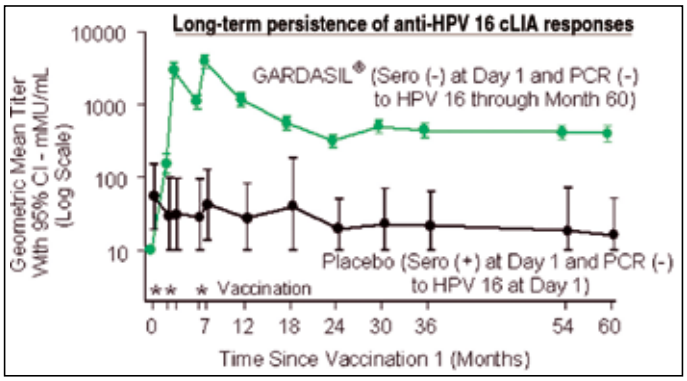
Gardasil trials have shown expected injection site symptoms of pain (84%), swelling (25%), erythema (25%) and pruritus (3%) during 1-5 days after injection. These results are only slightly more than symptoms reported from injection of the aluminium adjuvant alone.

Systemic adverse events 1 to 15 days after vaccination with Gardasil put fever incidence (10.3%) slightly above that reported for placebo (8.6%), with no significant difference on reported symptoms of nausea and dizziness.

During Phase III trials of Gardasil, a number of pregnancies were reported in both active (n=10,418) and placebo (n=9,120) trial participants – despite volunteers being asked not to conceive. There were equal numbers of congenital abnormalities in each group, with 15 in the Gardasil and 16 in the placebo group. Newborn anomalies were consistent with those generally observed in pregnancies in women aged 16-26 years (regardless of the vaccination's gestation timing).

Is vaccination effective?

Both vaccines are highly immunogenic. At 4 weeks after the 3rd dose, seroconversion rates are >99.5 % with antibody levels about 10–40 times that seen in natural infection. Antibody levels wane at 18-24 months but remain far higher than that seen in natural immunity (see graph).



Trial data have shown vaccination is highly effective when given prophylactically (i.e. before HPV exposure), preventing >90% of persistent infection caused by the HPV types within the vaccine, along with the resultant cervical disease and external genital warts. When women with prevalent infection or disease are included in the analysis, efficacy of the vaccine was lower.

Who should have it?

The vaccine will be most effective if given before sexual activity commences. Moreover, younger women (9-15 years) produce better antibody responses compared to older women (16-26 years).

In women already sexually active, the vaccine is of no benefit for disease already developed from HPV infections. A woman infected with one of the four HPV types in Gardasil still benefits from vaccination against the other three types. It is worth noting that from the baseline population characteristics in the trials of Gardasil (~20,000 females aged 16-26; 94 % sexually active), only <0.1% of those women had acquired all 4 types covered by the vaccine and 73% of the women were naïve to all 4 types. ■

References available on request

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