HPV VACCINES AND THE AUSTRALIAN HUMAN PAPILLOMAVIRUS (HPV) VACCINATION PROGRAM

Gerard Wain ■ Gynaecological Oncology, Westmead Hospital, Westmead, New South Wales.
Email: Gerard_Wain@wsahs.nsw.gov.au

Abstract

Australia was the first country in the world to commence a national vaccination program against human papillomavirus, using the quadrivalent human papillomavirus vaccine, Gardasil®. This program is soundly based on the natural history of human papillomavirus infection and utilises the vaccine that has been shown to be highly effective in preventing human papillomavirus related diseases. The program is a population-based strategy offering the vaccine to all Australian women, aged between 12 and 26 years. Preliminary evidence suggests that the program has achieved high coverage and high compliance. This foreshadows that Australian women will now form the first cohort of young women in the world to be protected against a wide range of human papillomavirus related diseases.

Australian women will be the first cohort of young women in the world to be vaccinated against a range of human papillomavirus (HPV) related diseases, including cervical cancer. The National HPV Program is funded by the Australian Government and was started in 2007. Under the program, the HPV quadrivalent vaccine, Gardasil®, will be provided free to girls and women aged 12 to 26 years. There are three aspects to the program: an ongoing vaccination program for all 12 year-old girls; a two year catch-up program for school girls aged 13-18; and a general practitioner based program for women aged 19 to 26 years. The school-based program started in April 2007 and the community-based program started in July of that year and will run until June 2009.

This program is expected to have a significant impact on the incidence of HPV infection and markedly reduce the clinical burden of HPV related disease in Australia. Boys and men are not included in the program at this stage because there is not yet enough clinical effectiveness data available in males, despite the public health grounds for including them.

The human papillomavirus

HPV infection is very common, with around 70% of both males and females showing evidence of HPV infection within five years of becoming sexually active. In 70 to 90% of cases, the infection will resolve within 36 months.[1] Infection with certain types of HPV is the major cause of invasive cervical cancers and their precursor lesions.[2] HPV infection itself is generally asymptomatic and is usually not recognised until patients are diagnosed with cervical dysplasia, cancer or genital warts.

Up to 79% of women worldwide are infected with HPV at some point in their lives. The peak incidence of infection is within the first five years of commencing sexual activity and studies in the US and UK have shown high rates of acquisition in young women. A woman's lifetime number of sexual partners is the most important risk factor, but the high transmission rate shows that even minimal sexual contact can result in infection.

Human papillomaviruses are small, non-enveloped DNA viruses that can affect cutaneous and mucosal epithelial tissues. Over 100 different types of HPV have been isolated and up to 40 of these types of HPV can infect the anogenital epithelium. HPV causes a variety of diseases in humans, ranging from benign warts to cancer of the epithelia (including the cervix, vagina, vulva, anus and oropharynx). Those HPV types associated with the development of cancer are called 'high risk' for oncogenicity. Other HPV types, such as HPV types 6 and 11 associated with genital warts, are considered 'low risk' for oncogenicity. HPV can be transmitted by direct skin-to-skin contact during all types of sexual activity. The viruses contain outer capsid components, referred to as the L1 and L2 viral components.

After infection, the protein products of two HPV genes, E6 and E7, bind to host cell growth proteins that have tumour suppressor functions and stop the normal arrest of cell division. In some cases of persistent infection, the HPV genome inserts into the host genome in a process known as integration.[3-4] After integration, E6 and E7 may be over-expressed, causing host squamous epithelial cells to proliferate in a less orderly fashion and acquire the cellular appearance of a high-grade squamous epithelial lesion (HSIL). A small proportion of HSIL clones of cells, which harbour persistent and commonly integrated HPV, become fully malignant and over time, manifest as invasive squamous cell carcinoma.[5]

HPV types are classified as high risk (oncogenic) or low risk (non-oncogenic) according to their risk of promoting oncogenesis. Approximately 15 high risk types have been linked to cervical, vaginal, vulval, anal, penile and head and neck cancers. Persistent infection of the

cervix with some high risk HPV types can cause cell changes that may lead to cervical cancer over a period of usually more than 10 years. High risk HPV types 16 and 18 are linked to 70 to 80% of cervical cancers and about 50% of high grade cervical pre-cancers in Australia.[6-7] HPV types 16 and 18 also account for about 25% of low grade cervical abnormalities.[8] Low risk HPV types include types 6 and 11, which are linked to approximately 90% of genital warts cases and around 10% of low grade cervical abnormalities. These HPV types can also cause recurrent respiratory papillomatosis, a rare but debilitating condition characterised by repeated growth of warts in the respiratory tract requiring surgery.

HPV vaccines

There are two vaccines currently available in Australia – a quadrivalent vaccine against types 6/11/16 and 18 called Gardasil® and a bivalent vaccine against 16 and 18 called Cervarix®. Both have been developed by recombinant genetic technology that allows expression of the major structural protein of HPV, the L1 protein that spontaneously assembles into virus-like particles (VLPs) which are both type specific and highly immunogenic.

Both vaccines contain VLPs, but the products differ in the types of HPV L1 proteins included as antigens, substrates used for production, adjuvant properties and in the final formulation. Antibodies raised to the VLPs provide protection against HPV infection, probably by transudation of IgG from serum to local mucosal/epithelial areas, especially at sites of trauma where HPV can otherwise gain access to basal epithelial cells.[9] Published efficacy studies suggest subtle but probably insignificant differences in prevention of type-specific HPV infections and disease.[10-11] The vaccines are not infectious, as they do not contain viral DNA, and Gardasil® has been safely administered to more than 22 million people worldwide. The vaccines prevent infection through the development of mucosal neutralising antibodies. They are prophylactic – not therapeutic – vaccines, and have no impact on pre-existing or previous infection. To date, Gardasil® is the only vaccine to be included on the Australian National HPV Vaccination Program.

High levels of antibodies have also been shown in young males and females following vaccination.[12-13] Immunogenicity responses one month after the three-dose vaccination regimen with Gardasil® show that the seroconversion rate is ≥99.5%, with antibody levels highest in 9 to 17 year-old boys and girls and 18 to 26 year-old women. There is currently no clinical efficacy data available in boys or men older than 15 years and only preliminary data showing efficacy of Gardasil® in women older than 26 years.

Bridging immunogenicity studies were conducted to link efficacy in young women aged 16 to 26 years to the younger populations. In most jurisdictions, recommendations for vaccination have been made for girls aged approximately 12 years, as this population will mount a very effective immune response to the vaccine and will be most unlikely to have prior exposure to HPV infection. Several jurisdictions, including Australia, have also recommended catch-up programs for women aged 13-26 years.

Rationale for the Australian HPV vaccination program

Implementation of a vaccination program for 12 to 26 year-old women has shown to be cost-effective in Austalia.[14] It is estimated that the vaccination program will reduce the lifetime risk of cervical cancer by 48%, compared to the current screening system. This estimate is based on data from the National Cervical Screening Program in Australia, 100% vaccine effectiveness, lifetime duration of efficacy and 80% coverage. The vaccine should also substantially reduce the incidence of cervical precursor lesions and the related interventions.

The administration of all three doses is important for optimal protection from the vaccine, so compliance needs to be encouraged. Logistics around the school based program have involved teams of trained nurses visiting schools on an organised rotational basis. The school-based program has been administered over the course of a single school year to reduce the potential for missed doses. Preliminary information regarding the program suggests that high coverage rates have been achieved in the school vaccination program, with high levels of compliance with second and third doses.[15]

No new vaccine has ever entered clinical practice with a known duration of protection. Therefore, the exact duration of protection from the current vaccines will not be known for many years. However, to date, research has shown that Gardasil® confers protective immunity and efficacy for at least five years and there is no indication currently that boosters will be needed. In addition, there is evidence of an immune memory response, so long-term protection is likely. Clinical trials are continuing and the results will be monitored to determine whether booster doses will be needed in the future.

A National HPV Vaccination Program Register is being developed by the Australian Government to collect data about the program. Personal details identifying the patient will be kept confidential and information will not be sought about the patient's sexual history. Personal information collected will be used to evaluate the impact of the HPV Vaccination Program on cervical cancer rates, to issue reminders if the course is incomplete, to issue confirmation the course is complete and to contact vaccine recipients should booster doses become required.

Conclusion

The National HPV Vaccination Program represents an additional prevention strategy against cervical cancer and other HPV-related diseases and will complement the National Cervical Screening Program. All eligible women should be encouraged to participate in the program and obtain the benefits of this highly effective vaccine.

References

1. Frazer I. Advances in prevention of cervical cancer and other human papilloma related diseases. Ped Infect Dis 2006; 25: S65-S81.
2. Braly P. Preventing cervical cancer. Nat Med 1996; 2: 749–751.
3. Arends MJ, Buckley CH, Wells M. Aetiology, pathogenesis, and pathology of cervical neoplasia. J Clin Pathol 1998; 51: 96–103.
4. Flaitz CM, Hicks MJ. Molecular piracy: the viral link to carcinogenesis. Oral Oncol 1998; 34: 448–453.
5. Stoler MH. Human papillomaviruses and cervical neoplasia: a model for carcinogenesis. Int J Gynecol Pathol 2000;19:16–28.
6. Brestovac B, Harnett GB, Smith DW et al. Human papillomavirus genotypes and their association with cervical neoplasia in a cohort of Western Australian women. J Med Virol 2005; 76: 106-110.
7. Stevens MP, Tabrizi SN, Quinn MA et al. Human papillomavirus genotype prevalence in cervical biopsies from women diagnosed with cervical intraepithelial neoplasia or cervical cancer in Melbourne, Australia. Int J Gynecol Cancer 2006; 16: 1017-1024.
8. Clifford GM, Franceschi S, Diaz M et al. HPV type-distribution in women with and without neoplastic diseases. Vaccine 2006; 24 suppl 3: s26-34.
9. Stanley M, Lowy DR, Frazer I. Prophylactic HPV vaccines: Underlying mechanisms. Vaccine 24S3 (2006) S3/106-S3/113.
10. The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. NEJM 2007, 356:1915-1927.
11. Paavanen J, Jenkins D, Bosch F et al. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III, double-blind randomised controlled trial. Lancet 2007, 369:2161-2170.
12. Block SL, Nolan T, Sattler C et al. Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus (types 6,11,16, and 18) L1 virus-like particle vaccine in male and female adolescents and young adult women. Paediatrics 2006; 118: 2135-2145.
13. Reisinger et al. Safety and Persistent Immunogenicity of a Quadrivalent Human Papillomavirus Types 6,11,16,18 L1 Virus Like Particle Vaccine in pre Adolescents and Adolescents: A Randomised Controlled Trial Pediatr Inf Dis J 2007; 26: 201-209.
14. Kulasingam S, Connelly L, Conway E et al. A cost-effectiveness analysis of adding a human papillomavirus vaccine to the Australian National Cervical Cancer Screening Program. Sexual Health, 2007, 4, 165–17.
15. New South Wales, Department of Health. [monograph on the internet] NSW School based Immunisation Program Results – HPV Results: 1 January 2007-16 November 2007. Available from: http://www.health.nsw.gov.au/PublicHealth/Immunisation/school_prog/results_index.asp [accessed 16/4/08].