The National HPV Vaccination Program

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The new National HPV Vaccination Program is expected to reduce markedly the burden of HPV related disease in Australia.

In the new National Human Papilloma Virus (HPV) Vaccination Program the HPV vaccine, Gardasil, will be provided free to girls and women aged 12 to 26 years. The school-based program started in April this year and the community-based program will start in July. 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 are not yet enough effectiveness data available for these groups.

HPV infection

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 squamous cell carcinomas and adenocarcinomas and their precursor lesions.[2] HPV infection is generally asymptomatic and is usually not recognised until patients are diagnosed with cervical dysplasia, cancer or genital warts.

The human papillomavirus (HPV)

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 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.

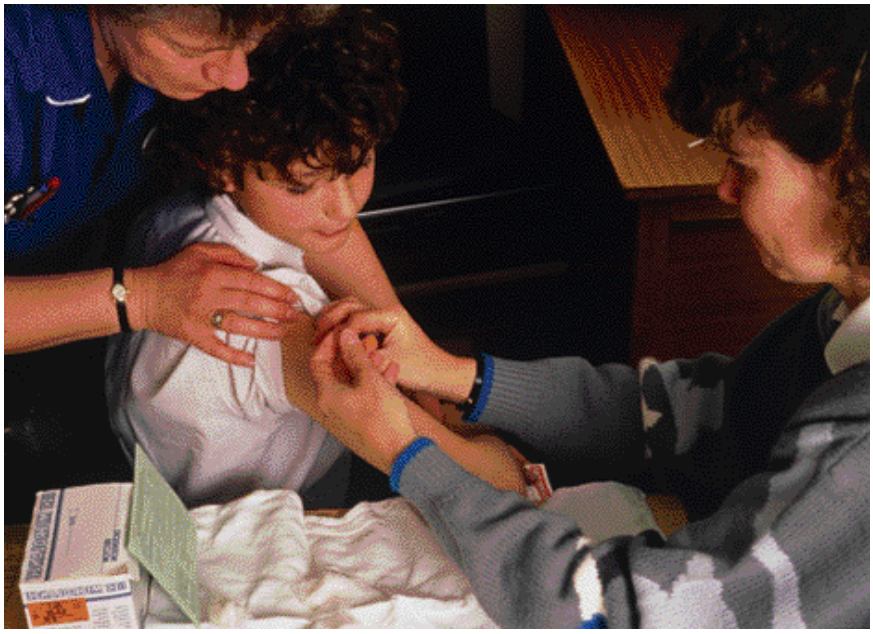
HPV and neoplasia

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 overexpressed, 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 cells, which harbour persistent and commonly integrated HPV, become fully malignant and, over time, manifest as invasive squamous cell carcinoma.[5]

HPV types

HPV types are classified as high risk (oncogenic) or low risk (non-oncogenic) according to their risk of promoting oncogenesis.

Approximately 15 high risk HPV types



PHOTOLIBRARY

Figure. The school-based National HPV Vaccination Program will include girls aged 12 to 13 years (ongoing program) and, until the end of the school year in 2008, girls aged 13 to 18 years (school-based catch-up program).

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Who is covered by the National HPV Vaccination Program?

Following a recommendation from the Pharmaceutical Benefits Advisory Committee, the Australian Government agreed to implement a National HPV Vaccination Program, which started in schools in April 2007, and will start in general practices in July 2007. Under this program, the following groups will receive Gardasil free of charge:

- girls aged 12 to 13 years (ongoing program)
- girls aged 13 to 18 years, until the end of the school year in 2008 (school-based catch-up program)
- women aged 18 to 26 years (GP or community-based catch-up program). The full course of three doses must be completed before the end of June 2009 to be covered by the program. For girls aged 12 to 18 years who missed doses during the school-based program, catch up doses given by GPs are covered by the program in most cases, but contact your State or Territory Health Department for local regulations.

Vaccination is recommended for females before they become sexually active, as it is most effective before exposure to infection with HPV genital types 6, 11, 16 and 18. Women aged 18 to 26 years will benefit from vaccination if they have not been infected with HPV types 6, 11, 16 and 18. Even if infection has been acquired with one of these HPV types, protection against infection and disease from the other HPV types in the vaccine will be achieved. However, during the vaccination visit women should be counselled that the vaccine may be less effective if they have been exposed to HPV before vaccination.

Gardasil has been approved for use in boys aged 9 to 15 years, based on safety and antibody response, but the data on efficacy are not strong enough to warrant mass vaccination. Boys and men are not covered by the National HPV Vaccination Program.

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 precancers 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.

Epidemiology

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 USA 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.

HPV vaccines

Gardasil is distributed in Australia by CSL Ltd. A second HPV vaccine, Cervarix (manufactured by GlaxoSmithKline), which targets HPV types 16 and 18 only, is now licensed in Australia and expected to be available later this year. Both vaccines are recombinant, but Gardasil is produced in yeast cells and Cervarix is produced in insect cells. An application has been made by the manufacturer to the Pharmaceutical Benefits Advisory Committee (PBAC) to include Cervarix in the vaccination program.

Composition

HPV vaccines are made up of HPV L1 capsid proteins, which can self-assemble into virus-like particles. Gardasil contains type specific virus-like particles based on HPV types 6, 11, 16 and 18. The vaccines are not infectious as they do not contain viral DNA, and can therefore be safely administered.

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.

Efficacy

Gardasil is highly effective in the prevention of vaccine type-specific HPV disease, including type-specific infection, cervical, vaginal and vulval neoplasia, and genital warts, when a three-dose vaccination course is given to girls and women who have not been previously infected.[9,10] This efficacy has been shown to extend to at least five years.[11] No breakthrough HPV type 6,11,16 or 18 positive disease has been demonstrated in the vaccinated population. However, HPV disease caused by other viral types will not be prevented, so continued cervical screening is important.

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 show that the seroconversion rate is greater than 99.5%, with antibody levels highest in 9 to 15-year-old boys and girls.

There are currently no clinical efficacy data available in boys older than 15 years or men and 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. Efficacy studies are currently ongoing in women over 26 years and boys and men aged over 15 years. While there is no evidence to suggest that the vaccine would be harmful or lack efficacy in these groups, the potential clinical benefit still needs to be accurately defined.

Rationale for the vaccination program

The addition of a vaccination program with Gardasil for 12- to 26-year-old women has been shown to be cost-effective in Australia.[14] The vaccination program is estimated to reduce the lifetime risk of cervical cancer by 48%, compared with 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 sub-stantially reduce the incidence of cervical precursor lesions and the related interventions. The PBAC supported the introduction of the vaccine because it was shown to be cost-effective.

The box on page 56 lists the groups covered by the vaccination program.

Implications for GPs

Although the school-based program will not directly involve GPs, many parents are likely to discuss the program with their GPs. Also, some parents may choose to have their children vaccinated by their GP.

The community-based catch-up program will largely involve the administration of Gardasil through general practices. This part of the program covers women aged 18 to 26 years, and in most cases it will also cover girls aged 12 to 18 years who missed doses during the school-based program (contact your State or Territory Health Department for local regulations). This part of the program will operate from July 2007 to June 2009 and the full course of three doses must be completed before the end of June 2009. The vaccine is not approved for use in women aged 27 years or over, so women need to complete the course before they turn 27 years old.

Common questions about HPV vaccination

Why should patients be vaccinated at a young age?
The vaccine works best if given to girls and women before they have any contact with HPV. Also, antibody levels are highest in girls aged between 9 and 17 years, so this is an ideal time to give the vaccine for maximum benefit.

Should patients be vaccinated if they have had sexual contact?
Yes. Patients should still consider being vaccinated even if they have had sexual contact.

If patients have had sexual contact, they may still benefit from the vaccine because it is very unlikely that they will have been infected with all of the HPV types that are covered by the vaccine. Even if the patient has had a previous HPV infection, the vaccine will not cause any harm and there will be no increase in any potential side effects from the vaccine.

Should patients be vaccinated if they have had genital warts or an abnormal Pap smear?
Yes. Women who have had genital warts or an abnormal Pap smear result may still benefit from the vaccine, as the strain that caused the abnormality may be different from those included in the vaccine. Even if infected with one HPV type covered by the vaccine, the patient will still be protected against disease caused by the remaining three vaccine HPV types.

No reliable tests are available to check for past and current infections with the specific HPV types covered in the vaccine.

Should patients be screened for HPV before having the vaccine?
No, pre-immunisation screening is not helpful in determining whether a woman will benefit from HPV vaccination. Current laboratory tests are not able to detect vaccine type-specific HPV infection and will not identify whether the woman has had previous HPV infection or predict any likely benefit from vaccination.

Do patients still need Pap tests if they have been vaccinated?
Yes, because the vaccine does not cover all of the types of HPV that cause cervical cancer or abnormal Pap tests, it is important to continue regular screening. The current recommendations are that women should have a Pap smear every two years from the age of 18 or two years after having sex, whichever is later.

Clinical issues

Dosage and administration

Gardasil is administered intramuscularly, usually in the upper arm, as a series of three injections over a period of six months. The optimal schedule is:

- first dose – at elected date
- second dose – two months after the first dose
- third dose – six months after the first dose.

The vaccine has been shown to be effective if all three doses are given within 12 months. However, if doses cannot be completed within this time, the course should not be started again from the beginning. Missed doses should be given as soon as is practicable.

If a shorter vaccination schedule is necessary, the second dose should be given at least one month after the first dose and the third dose should be given at least three months after the second dose. Because of the April start date, shorter vaccination schedules are likely to be used in the school-based program during 2007.

Gardasil can be given at the same time as the hepatitis B vaccine, but at a different injection site. No data are available on the concomitant use of Gardasil with the diphtheria, tetanus and acellular pertussis (DTPa) vaccine or the varicella vaccine, but there is no reason to anticipate any adverse outcomes if they are given simultaneously in different injection sites.

Common questions about HPV vaccination are shown in the box on page 57.

Compliance

The administration of all three doses is important for optimal protection from the vaccine, so compliance needs to be encouraged. The school-based program will be administered over the course of a single school year to reduce the potential for missed doses.

Girls and women receiving the vaccine through general practices should be encouraged to use various reminder methods to ensure they complete the schedule. CSL has established a confidential web-based registration system whereby patients can register their details and receive reminders about the subsequent doses via email or SMS telephone messages (www.gardasilclub.com.au).

Contraindications and precautions

Hypersensitivity and allergy

Gardasil should not be given to patients with a history of severe allergic reaction to a previous dose of the vaccine or severe immediate hypersensitivity to any of the vaccine components (yeast, aluminium phosphate, sodium chloride, L-histidine, polysorbate and sodium borate). Patients with less severe types of yeast sensitivity can be given the vaccine, but this should be done under medical supervision.

Pregnancy

While there is no evidence to suggest that the vaccine adversely affects fertility, pregnancy or infant outcomes, Gardasil is not recommended for use during pregnancy. If the vaccine is inadvertently given during pregnancy, further doses should be deferred until after the birth; however, there is no need to consider termination. Gardasil can be administered to lactating women.

Febrile illness

Gardasil vaccinations should be delayed in patients who have a moderate to severe febrile illness until they have fully recovered.

Adverse events

In clinical trials, the most commonly reported adverse events were mild to moderate injection site reactions (Gardasil, 83%; alum-containing placebo, 77%) including pain, swelling and erythema. The rate of systemic symptoms is no higher than with placebo, and few serious adverse events were reported during clinical trials. More information is given in the vaccine's product information.

Pain and swelling at the injection site can be relieved with paracetamol, and by placing a cool, moist cloth over the site.

Since the mass immunisation in schools has commenced, a number of media reports have described episodes of fainting, numbness and paraesthesia in Australian schoolgirls receiving the vaccine. These side effects are not unusual in mass vaccination campaigns. Hospitalisations following these episodes have been attributed to hyperventilation and anxiety.

The US Centers for Disease Control and Prevention (CDC) reported in February 2007 that after 2.1 million doses of Gardasil had been administered in the USA, the side effects were similar to those of other vaccines. They concluded that syncope is more common when any vaccine is administered to adolescents but stated that there was no more reason to associate Gardasil with syncope than any other vaccine.

Storage and handling

Supplies should be refrigerated at 2 to 8°C and administered soon after being removed from refrigeration. The vaccine should be shaken well before administration.

Booster doses

Research to date 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. Also, there is evidence of an immune memory response associated with Gardasil, 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.

The HPV Register

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 that the course is complete and to contact vaccine recipients should booster doses become required. Any person or parent/guardian will be able to opt-off the register if they wish.

GPs are encouraged to collect data when vaccinating girls aged 12 to 18 years who may have received doses in the school-based program. Data collection is not required when vaccinating women aged 18 to 26 years; however, the register will accept data for females in this age group if they elect to have their details included.

Conclusion

The National HPV Vaccination Program represents an additional prevention strategy against cervical cancer and other HPV related diseases. All eligible women should be encouraged to participate in

the program and obtain the benefits of this highly effective vaccine.

Further information

Many of the issues related to the clinical use of Gardasil were also discussed in the December 2006 issue of *Medicine Today*,[15] which included a Patient Handout.

Information on HPV and the HPV vaccine is available on the National Centre for Immunisation Research and Surveillance website at www.ncirs.usyd.edu.au and the Immunise Australia Program website at www.immunise.health.gov.au. Information about the National Cervical Screening Program is available on the Cancer Screening website at www.cancerscreening.gov.au. MT

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DECLARATION OF INTEREST: Dr Wain is Chair of CSL's Advisory Board for Gardasil and has been involved in some of the Merck clinical trials for the vaccine.