Gardasil in the prevention of cervical cancer

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The introduction of Gardasil, a vaccine against human papillomavirus, represents an important opportunity for primary prevention of HPV disease, including cervical cancers, precancerous lesions and genital warts.

The causal role of human papillomavirus (HPV) in cervical cancer has been firmly established.[1] More than 40 mucosal anogenital HPV types have been identified and at least 15 of these have oncogenic potential, causing nearly all cervical cancers and precancerous lesions.[2] HPV types 16 and 18 account for approximately 70% of cervical cancers and 50% of high grade cervical intraepithelial neoplasias (CIN 2, CIN 3).[3] HPV types 6 and 11, which are two of the low risk types, account for approximately 10% of low grade cervical abnormalities (CIN 1) and 90% of genital warts.

The availability of an HPV vaccine, Gardasil, in Australia has allowed for a paradigm shift in cervical cancer prevention. Until now, prevention was mainly achieved through detection of cervical abnormalities during screening. Now, physicians can deploy a primary prevention measure in the form of prophylactic vaccination to further reduce the burden of both cervical cancers and precancerous lesions.

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What is Gardasil?

Gardasil is a quadrivalent HPV recombinant vaccine that protects against disease caused by HPV types 6, 11, 16 and 18. It is the first vaccine to be approved for use in the prevention of anogenital cancers, precancers or warts related to HPV infection.

Gardasil is composed of four types of L1 protein (the major capsid protein of HPV), one from each of the different types of HPV. The L1 protein can self-assemble into virus-like particles that closely resemble the normal structure of HPV but do not contain viral DNA and are therefore not infectious. Protection against disease is assumed to be due to the development of humoral immune responses via serum neutralising IgG.

How is the vaccine administered?

Gardasil is administered intramuscularly as three separate doses. According to the recommended dosing schedule, the second and third doses should be given two and six months after the initial dose. Patients are encouraged to adhere to this schedule, but some flexibility is acceptable. In clinical trials, efficacy has been demonstrated in individuals who received all three doses within a one-year period.[4,5] When it is necessary to use a different vaccination schedule, the second dose should be administered at least one month after the first and the third dose should be administered at least three months after the second.

PHOTOLIBRARY

Figure. Coloured scanning electron micrograph of a cervical cancer cell dividing.

Who should be vaccinated?

Gardasil is approved in Australia for use in females aged 9 to 26 years for the prevention of cervical, vulvar and vaginal cancers, precancerous or dysplastic lesions, genital warts and infection caused by HPV 6, 11, 16 and 18.[6] The vaccine is also indicated for use in males aged 9 to 15 years for the prevention of infection caused by HPV 6, 11, 16 and 18.[6]

Ideally, vaccination should occur before sexual activity is commenced. However, individuals who are already sexually active should be vaccinated at the earliest opportunity.

How effective is Gardasil?

Worldwide clinical trials of Gardasil efficacy have involved approximately 20,000 women aged 16 to 26 years of age; participants had a lifetime history of up to five sexual partners and most were sexually active. Vaccination with Gardasil was shown to prevent 100% of high grade cervical precancers and noninvasive cancers (CIN 2, CIN 3 and adenocarcinoma *in situ*) associated with HPV types 16 and 18.[4,5] This endpoint has been accepted by the WHO and the US Food and Drug Administration as the appropriate endpoint for

prophylactic HPV vaccine clinical trials.[7] Clinical trials of efficacy against disease in males and females over 26 years of age have not yet been completed; it is anticipated that results from these smaller studies will be available in 2008.

In these key efficacy studies, Gardasil also prevented 99% of external genital lesions, including genital warts, vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VaIN) related to the vaccine HPV types.

What about immunogenicity?

Gardasil has demonstrated good immunogenicity, inducing high and persistent antibody levels. In women aged 9 to 26 years, seroconversion rates against HPV 6, 11, 16 and 18 are greater than 99% one month after the third dose.[8] The antibody levels induced by the vaccine have been shown to be substantially higher than those measured in women with evidence of having mounted an immune response due to natural HPV infection.[8]

Should sexually active women be vaccinated?

Although HPV is contracted through sexual contact, being sexually active does not always mean that a woman has been infected with the vaccine HPV types. Most women in the clinical studies where effectiveness was demonstrated had been sexually active prior to vaccination. Therefore, prior sexual activity should not preclude vaccination.

Of the women included in the Gardasil efficacy trials, 27% were either seropositive or HPV-DNA positive to at least one of the vaccine HPV types at enrolment. However, most of these women were positive for only one of the four types and would therefore benefit from vaccination against the remaining HPV types in a quadrivalent vaccine. In fact, only one woman in the trial population was positive for all four vaccine HPV types.

Do I need to screen my patients for HPV infection prior to vaccination?

There is no practical or reliable method of screening for prior HPV exposure. The US Advisory Committee on Immunisation Practices of the Centers for Disease Control and Prevention (CDC) has provisionally recommended that the decision to vaccinate should not be based on the results of Pap testing, HPV-DNA testing or HPV serological testing. Further information is available on the CDC website (www.cdc.gov/nip/recs/provisional_recs/default.htm).[9]

Will vaccination eliminate the need for Pap testing?

Vaccination with Gardasil offers protection against the high risk HPV types responsible for approximately 70% of cervical cancers. However, at least 13 other genotypes are responsible for the remaining 30% of cases. In addition, some women who receive the vaccine will have already been infected with one or more vaccine types – the vaccine will not be efficacious in altering the natural history of these established infections and some may go on to develop into precancers and cancers. For these reasons, it is important to ensure that women of all ages continue to receive regular Pap tests even after vaccination.

What about cross protection?

Data from a recent *in vitro* study have demonstrated that the antibodies induced by Gardasil prevent, or neutralise, the ability of HPV 31 and 45 virus-like particles (synthetic viruses) to infect cells.[10] The cancer-causing HPV types 31 and 45 are directly related to HPV types 16 and 18 and together account for approximately 8 to 9% of all cervical cancers. The study authors concluded that vaccination with Gardasil induced antibody responses capable of neutralising vaccine-type and related non-vaccine HPV type infection. Further studies will assess whether these findings translate into protection from disease.

How long does protection from Gardasil last?

There is currently five years of efficacy data for Gardasil – one of the longest available efficacy data for any vaccine at launch. Recent research has demonstrated the presence of a memory response suggesting long term protection.[8] Sentinel cohorts have also been established to further monitor the duration of efficacy.

What about precautions and interactions?

As with any injectable vaccine, appropriate medical treatment should always be available when Gardasil is administered in case of rare anaphylactic reactions. Low grade fever and mild upper respiratory tract infections are not generally contraindications to vaccination. Patients who have impaired immune responsiveness may have a reduced antibody response to active immunisation. The vaccine should be used with caution in patients with thrombocytopenia or any coagulation disorder because bleeding may occur following intramuscular administration in these individuals.

In clinical trials, women found to be pregnant before completion of the three-dose regimen were instructed to defer completion of the vaccination schedule until resolution of the pregnancy.[4] The outcomes of these pregnancies were comparable between placebo and vaccine groups. Gardasil has been designated Category B2 regarding use in pregnancy by the Australian Drug Evaluation Committee (ADEC). The vaccine may be administered to lactating women.

Gardasil is not affected by the use of analgesics, anti-inflammatory drugs, antibiotics, vitamin preparations or corticosteroid medications. The immune response is not affected by hormonal contraceptives. Patients taking immunosuppressive agents may not respond

optimally to active immunisation. Gardasil may be administered at the same time (but at a different site) as hepatitis B vaccine.

What are the common side effects?

Gardasil is generally well tolerated. Reported side effects include injection site reactions such as pain, swelling and erythema, although these were mostly mild to moderate in intensity. Fever has also been reported.

What does the vaccine cost?

Gardasil is currently available on private prescription at a cost of about $150 per dose from a retail pharmacy. An application has been submitted to the Pharmaceutical Benefits Advisory Committee (PBAC) for funding under the National Immunisation Program. Current indications are that a Government-funded program for limited cohorts is expected to commence at some point during 2007.

Conclusion

Australia has one of the most successful cervical cancer screening programs in the world. Although the incidence of cervical cancer is low, the incidence of precancerous abnormalities is considerable. In 2004, approximately 14,500 women were diagnosed with high grade abnormalities (on histology) requiring surgical treatment, and a further 16,500 women were diagnosed with low grade abnormalities requiring further investigation and/or follow up.[11] In combination with regular cervical screening, the availability of a prophylactic vaccine represents a unique opportunity to further reduce the burden of cervical cancer and precancers. 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.