

Warts and All

HPV Infection and the HPV Vaccine



Last year in Canada, 400,000 women were diagnosed with cervical dysplasia. There were 14,000 new cases of cervical cancer resulting in nearly 400 deaths. In August 2006, Health Canada approved the first-ever vaccine against human papillomavirus (HPV), known to cause most cervical cancer cases. The quadrivalent HPV 6,11,16,18 recombinant vaccine, Gardasil™ was approved for use in females aged 9 to 26 years. This article presents details about this vaccine, as well as updated information on HPV infection from the *Canadian Guidelines on Sexually Transmitted Infection* 2006 Edition.

HPV and cervical cancer

There are more than 130 known types of HPV, the majority of which cause asymptomatic or subclinical infections. At least 40 of these HPVs are known to be sexually transmitted, infecting the anogenital epithelium via skin-to-skin contact. The most common sites of infection include the cervix, vagina, vulva and anus in females, and the penis and anus in males. HPV infections are often acquired at a young age (adolescents and young adults); however, men and women of all ages can be affected.

Prevalence of HPV infection is as high as 29% in young women and approximately 70% of the population will be affected over the course of their lives. More than 80% of these infections are self-limiting, resolving spontaneously within 18 months to two years after exposure. Use of condoms does not completely abolish the risk of HPV infection, but greatly reduces it (e.g., from 89.3 infections per 100 patient-years in infrequent condom users to 37.8 in consistent condom users, in one study of newly sexually active women.)

Approximately 15 sexually transmitted HPVs are classified as high risk because of their associated risk with the development of cancer of the cervix (see table below). HPV infection can lead to squamous intraepithelial lesions (cervical dysplasia) which often resolves once the infection clears. However, in some women, persistent infection with these high risk HPVs can lead to cervical cancer. HPV 16 and 18 are thought to be responsible for at least 70% of cervical cancer cases and are also associated with a risk of cancers of the vulva, vagina, anus or penis, as well as some head and neck cancers (e.g., cancer of the tonsils). Cancer can develop up to 20 years after the initial infection with HPV.

The strains of HPV (e.g., 6 and 11) that cause genital warts (condylomata accuminata) do not cause cervical cancer. The number and size of warts will vary over time before resolving spontaneously in 90% of patients within 2 years. Treatment may be used for symptom relief (e.g., for bleeding, pruritis or discharge), but also for the psychological burden to the patient.



HPV Vaccine

The goal of the Gardasil™ vaccine is to prevent primary or persistent infection with four strains of HPV (6, 11, 16 and 18) and thus lower the risk of cervical and other cancers, as well as genital warts. It is approved for females between 9 and 26 years of age. Ideally, the vaccine should be given to girls before they become sexually active and before possible contact with HPV 6, 11, 16 or 18. It should be noted that even if infection has occurred with any of these HPV types, the vaccine is still effective against the others.

There is at least one other HPV vaccine being tested in phase III trials (Cervarix™ which protects against strains 16 and 18, and may also protect against other oncogenic strains). In addition, trials are underway for *therapeutic* HPV vaccines, which will treat existing infections.

Risk factors:

The risk of HPV infection is known to increase with the number of lifetime sex partners. Other risk factors have been suggested but their role is less clear:

- Smoking.
- Higher number of pregnancies.
- Infection with other sexually transmitted infections (STI), such as HIV, chlamydia trachomatis, or herpes simplex virus-2.
- Poor diet (e.g., insufficient antioxidants).
- Immunosuppression due to HIV/AIDS, organ transplantation or use of immunosuppressive drugs.
- Sexual intercourse at a young age, with those infected or with multiple partners.
- Genetic predisposition.
- Non-use or inconsistent use of condoms.

HPV genotypes and associated clinical conditions		
Association with cervical cancer	Genotypes	Most likely clinical conditions
Low-risk	<ul style="list-style-type: none"> • Most common: 6 and 11 • 40, 42, 43, 44, 54, 61, 70, 72, 81 and CP6108 	Condylomata accuminata (genital warts)
Probable high-risk	<ul style="list-style-type: none"> • 26, 53 and 66 	Precancerous or cancerous lesions
High-risk	<ul style="list-style-type: none"> • Most common: 16, 18 • 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82 	Precancerous or cancerous lesions

Adapted from: Canadian Guidelines on Sexually Transmitted Infections 2006 Edition. ©Public Health Agency of Canada, 2006. http://www.phac-aspc.gc.ca/std-mts/sti_2006/pdf_2006_e.html (accessed November 20, 2006)

Dosage Schedule

The vaccine is given in three doses according to the following schedule:

- First Dose—minimum age is 9 years old.
- Second dose—two months after the first dose (minimum 4 weeks).
- Third dose—six months after the first dose (minimum 12 weeks).

The HPV vaccine is given intramuscularly and may be administered in the thigh or arm. It can be given at the same time as other vaccines and all three doses are required for maximum effectiveness. If the second dose is not given within the recommended time period, it should be given as soon as possible. The third dose should then be given no sooner than 12 weeks later. A Papanicolaou (Pap) smear and screening for HPV infection are not necessary prior to vaccination.

The cost is not currently covered by any provincial health plans. The individual provinces will need to decide whether it will be offered free of charge. The current cost in Ontario is approximately \$500 for the three-dose series.

Controversies

Despite the demonstrated safety and efficacy of the vaccine, there has been some concern about immunizing preadolescent girls against sexually transmitted infections. It has been suggested that this practice may undermine efforts to encourage abstinence in teenagers, but there is currently no evidence for this possibility. Vaccination for hepatitis B, a potentially sexually transmitted infection, is administered routinely to seventh graders (12 years of age) in Ontario and other provinces, demonstrating a precedent of acceptance of STI vaccination. Parental and patient education on HPV infections is an integral component of successful HPV vaccination.

Gardasil™ offers coverage for two oncogenic strains (accounting for 70% of cervical cancers) and two strains that cause genital warts. Apparently, Cervarix™ may cover additional oncogenic strains (accounting for 90% of cervical cancers), but will not cover strains causing genital warts. Parents and patients will need to decide what type of HPV coverage they wish to have.

What we know about Gardasil™

- ✓ The vaccine is nearly 100% effective in preventing infection by the four targeted strains and the development of cervical intraepithelial neoplasm (CIN) lesions associated with these strains.
- ✓ The vaccine is well-tolerated with few reported side effects. The most commonly reported side effect is soreness around the injection site. Swelling, erythema, fever and pruritis have also been reported.
- ✓ The vaccine maintains 98% seropositivity at 4.5 years.
- ✓ There is some evidence that the vaccine may also neutralize strains 31 and 45, which account for an additional 8–9% of cervical cancers.
- ✓ Existing infections, genital warts, precancerous conditions or cancers are not treated by the vaccine.

What we don't know

- ? Efficacy of the vaccine in boys or women over the age of 26 years. (There is insufficient research to recommend the vaccine in these groups. Vaccinating boys may help to prevent rare cancers and genital warts, as well as to indirectly protect girls with whom they have sexual contact.)
- ? Need for a booster after five years.
- ? Safety in pregnant women. (The vaccine is not currently recommended for this group, although no problems for pregnant women or babies have been reported.)

Guidelines

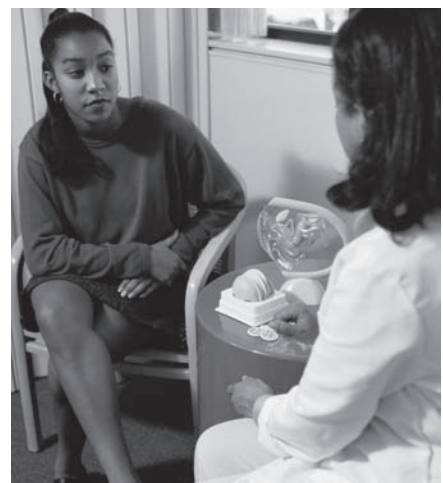
At the time of writing, the National Advisory Committee on Immunization (NACI) has not yet made their recommendations regarding Gardasil™. This report is expected by the end of 2006. The Society of Obstetricians and Gynecologists of Canada (SOGC) has issued an interim statement supporting HPV vaccination and is in the process of reviewing and updating recommendations about HPV and cervical cytology screening.

The American Advisory Committee on Immunization Practices has recommended that the vaccine be offered routinely to all girls aged 11 and 12 years, and that a catch-up vaccination series should be offered to females between 13 and 26. They suggest that recommending immunization of 9 and 10 year-old girls should be left to the discretion of the physician. They also note that the vaccine can be offered even if the potential recipient has a history of an abnormal Pap smear, a positive HPV test or genital warts.



Pap smears

Administering the HPV vaccine does not obviate the need for cervical cancer screening, since the vaccine does not protect against all cervical cancer-causing HPV types. In Canada, the incidence and death rates of cervical cancer have declined by 50% and 60% respectively since 1977. These decreases are thought to be due, at least in part, to an increase in the proportion of women having routine Pap tests. Current recommendations for PAP screening remain unchanged for women who receive HPV vaccination. ■



The Bottom Line

- Human papillomavirus, strains 6, 11, 16 and 18, are responsible for 70% of cervical cancer cases and 90% of genital warts.
- The HPV vaccine, Gardasil™, prevents nearly all cases of cervical cancer and genital warts caused by these high-risk HPV strains.
- The HPV vaccine does not replace the need for cervical cancer screening with Pap testing.

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