

Chapter 11: The HPV Vaccines, Liquid Based Cytology and HPV Testing

On completion of this section, the learner will be able to describe the following:

1. The Human Papillomavirus (HPV) Vaccines
2. Liquid Based Cytology
3. HPV Testing

Learning Objectives

The HPV Vaccines^{1,2}

Three HPV vaccines have been approved for use in Canada:

Vaccine type	HPV types covered	Protects against:
Cervarix	16, 18	Over 70% of cervical cancers
Gardasil-4	6, 11, 16, 18	Over 70% of cervical cancers and 90% of genital warts
Gardasil-9	6, 11, 16, 18, 31, 33, 45, 52, 58	90% of cervical cancers and 90% of genital warts

Recommendations

The National Advisory Committee on Immunizations (NACI) has made several recommendations since the vaccines were approved for use in Canada. The following is a summary reflecting the most recent recommendations as of January, 2012.

Gardasil-4 and Cervarix are recommended for:

- **Females between 9 and 13 years of age.** Most females in this age group have not yet been sexually active. Efficacy of the vaccine is greatest when it is administered prior to HPV exposure.
- **Females between 14 and 26, who may have:**
 - already been sexually active. These groups may not yet have been exposed to HPV infection and are very unlikely to have been exposed to all four HPV types for which the vaccine protects against.
 - been exposed to HPV infection.
 - already had previous Pap test abnormalities, including cervical cancer and genital warts. Previous or existing HPV infection could very well be from HPV types that are not included in the vaccine. If, however, any infection is from HPV types 6, 11, 16 or 18, there is no evidence that suggests the vaccine will have any therapeutic effect on existing infection or cervical dysplasia.

Gardasil-4 and Cervarix may also be administered to females between the ages of 26-45.

Gardasil-4 and Cervarix are not recommended for the following populations:

- **Females under the age of 9.** Neither efficacy nor duration of protection is known for this group. The vaccine is therefore not recommended for females under the age of 9.
- **Pregnant women.** Research on vaccination of pregnant women is limited. Thus, vaccination of these groups should be avoided. If the vaccination series is initiated with an unknown pregnancy, the series of vaccinations should be postponed until after delivery. Intervention in these circumstances has not been shown to be necessary.
- **Immunocompromised persons.** Gardasil may be delivered to individuals who are immunosuppressed; however, the efficacy of the vaccine in these populations is unknown. Immunocompromised persons should be aware that response to Gardasil may be less effective than efficacy for individuals from the average population.
- **Males (Cervarix only).** Cervarix is not yet recommended for males.

To learn more about the NACI recommendations for males, visit the Public Health Agency of Canada website.

Dosage and Schedule

The vaccines are given in 2 or 3 separate doses of 0.5 mL as follows:

- Gardasil: 0, 2 and 6 month intervals.
- Cervarix: 0, 1 and 6 month intervals

They are administered intramuscularly in the deltoid or anterolateral upper thigh.

Vaccine Efficacy

The HPV vaccines are most effective when given to females before they start having sexual contact. If received before exposure to the HPV types covered in the vaccines, it will be almost 100% effective in preventing infection from the HPV types that the vaccine provides protection against. Studies show that females who have already been sexually active may also benefit from receiving the vaccine as it is unlikely they would have been exposed to all HPV types covered in the vaccines. Studies are ongoing to determine if a booster is required to enhance the duration of protection.

Safety

The vaccines are safe. Health Canada has approved the vaccines based on a scientific review of their quality, safety and effectiveness. As with all vaccines, side effects may occur including rare adverse events, e.g. allergic reactions, nausea, dizziness. The most common side effects are soreness, pain and swelling at the injection site.

What is in the vaccines?

The HPV vaccines contain proteins that act like the HPV virus. The body starts making antibodies and white blood cells to fight against these virus-like particles. This builds up immunity to the HPV virus. There is no active virus in the vaccines. Nor are there any antibiotics or preservatives, such as mercury or thimerosal.

Pap Tests and the HPV Vaccine

All three vaccines have demonstrated to be very effective in preventing HPV infection. There are, however, other HPV types not covered in the vaccines that can cause cervical cancer. Women who receive the HPV vaccine therefore, still need to have regular Pap tests as recommended by their provincial program.

The Manitoba HPV Immunization Program

In the 2008-2009 school year, Manitoba Health introduced a vaccine program for grade 6 girls. In 2016, Manitoba Health added grade 6 boys to the Manitoba HPV Immunization Program. The program is voluntary, and is administered by public health nurses.

Before any student is immunized, parents and legal guardians receive information about HPV and the vaccine, and a consent form indicating permission for their child to receive the vaccine.

Vaccine Cost

Females and males in the Manitoba HPV Immunization Program can access the vaccine (Gardasil-4) at no cost through the school-based program, their regular health care provider or a pharmacist. The program includes:

- All females and males in grade 6 (school-based program),
- Females who missed the vaccine in grade 6 and are born on or after January 1, 1997, Females born between 1986 and 2005 who started the vaccine series before March 31, 2014,
- Males who missed the vaccine in grade 6 and are born on or after January 1, 2005, and
- Males born between 2002 and 2004.

Females and males not in the Manitoba HPV Immunization Program can purchase the vaccine through their health care provider, public health nurse or pharmacist. A prescription is required.

Liquid Based Cytology³

With Liquid Based Cytology (LBC), a sample of cells is taken from the cervix using a broom-like device. The cervical sample is deposited in a liquid medium and sent to the laboratory for examination.

Research shows that LBC is not more sensitive than conventional cytology.⁴ However, because it removes most artifacts and other obscuring elements, the frequency of unsatisfactory results is reduced. LBC also allows for automated cytology reading and provides the foundation to perform HPV testing.

HPV Testing^{2,5}

HPV testing is molecular DNA testing for the detection of oncogenic HPV types that can cause cervical cancer and its precursors. HPV testing can be applied in the following settings: i) Primary screening for high-risk HPV types alone or in combination with cytology, ii) triage of women with equivocal cytological results (HPV reflex testing), or iii) follow-up of women treated for precancerous neoplastic lesions to determine success or failure of treatment (test of cure).

The benefits of HPV testing have been well demonstrated and include:

- Compared with the Pap test, HPV testing is much more sensitive to detect high-grade precancerous lesions.
- HPV testing is better at detecting cervical adenocarcinoma

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- HPV testing provides the opportunity to facilitate self-sampling for unscreened populations
 - HPV testing allows for a longer screening interval and earlier cessation of screening
 - HPV is testing more attractive as vaccinated cohorts reach screening age

Three approaches have been developed to detect HPV DNA or RHA in cervical specimens.

1. HPV Generic Assays

HPV generic tests detect the presence of a group of high-risk HPV types without identifying specific HPV types. The following two generic assays are currently licensed in Canada for HPV diagnosis.

- a. The **Hybrid Capture system (HC2)** detects the presence of a group of 13 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, or 68). HC2 is manufactured by Qiagen Incorporated and is recognized as the gold standard in the category of generic HPV tests. HC2 is used for triage of women with atypical squamous cells of undetermined significance (ASC-US) Pap test results.
- b. The **Amplicolor HPV test** is manufactured by Roche Diagnostics and detects the presence of the same high-risk group of HPV types in the Hybrid Capture system. The value of Amplicolor has not been established for primary cervical cancer screening.

2. Full Genotyping Assays

Full genotyping tests detect if HPV is present and identify the type(s) of HPV. Currently, there is only one HPV test in this category and it is being used solely as a research tool.

- a. The **Linear array** is manufactured by Roche Diagnostics and detects the presence of 36 high and low risk types of HPV. These include HPV types 6, 11, 16, 18, 26, 31, 34, 35, 39, 40, 42, 44, 45, 51-54, 56, 58, 59, 61, 62, 66-73, 81-84 and 89.

3. Partial Genotyping Assays

Partial genotyping tests will specifically identify if HPV types 16 and/or 18 are present, as well as detect the presence of several high risk HPV types as a group (without identifying the specific type). The following three partial genotyping assays are currently licensed in Canada for HPV testing:

- a. The **Cobas 4800** HPV test is manufactured by Roche Diagnostics and separately detects high-risk HPV types 16 and 18, as well as a high risk group of 12 genotypes (HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68).
- b. The **Cervista HR HPV** and **Cervista 16/18 HPV** tests are manufactured by Hologic Incorporated. First, the Cervista HR HPV test is used to test for a group of 12 HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 5, 66 and 68). If the Cervista HR HPV test is positive, then a second test, Cervista 16/18 HPV is applied. More large-scale studies are still needed on this test before using it for cervical cancer screening.
- c. The **Abbott Realtime High Risk HPV test (Abbott Molecular)** is manufactured by Abbott and detects high-risk HPV types 16 and 18 separately as well as a group of 12 high-risk types of HPV (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). As with the Cervista test, more studies are needed before implementing the Abbott Realtime High Risk HPV test into a cervical cancer screening program.

Currently, HPV testing is not offered routinely in Manitoba.

	Recommended Reading
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[CervixCheck Resources](#)

[National Advisory Committee on Immunization](#)

[Manitoba Health](#)

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| <ol style="list-style-type: none">1. What are the four HPV types that Gardasil-4 protects against when administered prior to sexual activity?2. Who are the HPV vaccines recommended for? Who is it not recommended for?3. What are the benefits to using liquid based cytology?4. Describe the three ways that HPV testing can be used. | Chapter 11
Self-Test |
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References

¹ National Advisory Committee on Immunization. (2007). Statement on Human Papillomavirus vaccine. Retrieved March 4th, 2009 from Public Health Agency of Canada Website: <http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/07vol33/acs-02/index-eng.php>

² National Advisory Committee on Immunization (2012). Update on Human Papillomavirus Vaccines. Retrieved February 6, 2012 from Public Health Agency of Canada Website: <http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/12vol38/acs-dcc-1/index-eng.php>

³ Canadian Agency for Drugs and Technologies in Health. (2008). Liquid-based techniques for cervical cancer screening: Systematic review and cost-effectiveness analysis. Retrieved March 4th, 2009 from: http://cadth.ca/media/pdf/333_LBC-Cervical-Cancer-Screening_Review.pdf

⁴ Annals of Internal Medicine (2011). Liquid-Based Cytology and Human Papillomavirus Testing to Screen for Cervical Cancer: A Systematic Review for the U.S. Preventive Services Task Force. Retrieved July 16, 2012 from: <http://annals.org/article.aspx?articleid=1033158>

⁵ Canadian Partnership Against Cancer, Screening Portfolio (2012). HPV Testing for Cervical Cancer Screening, Expert Panel: Summary of Evidence. Retrieved June 6th, 2012 from: http://cancerview.ca/idc/groups/public/documents/webcontent/hpv_testing_final.pdf