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March 31, 2014

Dear Health Care Provider:

Human Papillomavirus (HPV) Eligibility Criteria

Effective March 31st 2014, all Manitoba girls and women in Grade 6 and those born on or after January 1st 1997 are eligible to receive the HPV vaccine series free-of-charge. Girls or women with increased risk of HPV infection who started the 3-dose series before March 31st 2014 will be eligible to finish the series free-of-charge.

New and emerging research on HPV and the vaccines that protect against it continues to grow. Manitoba is currently exploring the evidence in support of immunizing additional cohorts, including males and individuals with high-risk medical conditions (e.g. immune deficiency). In the meantime, Merck, the manufacturer of the HPV vaccine Gardasil®, is developing a 9-valent HPV vaccine which is intended to provide even more protection against cervical cancer than the original 4-valent Gardasil® vaccine.

Manitoba Health, Healthy Living and Seniors collaborates with public health experts across Canada through federal, provincial and territorial networks and committees in order to develop national vaccine recommendations that provincial and territorial Ministries of Health use to inform publicly-funded vaccine programs. The vaccine experts and stakeholder membership of Manitoba's Provincial Vaccine Advisory Committee then systematically reviews the national recommendations, along with other key pieces of evidence and research, and makes a recommendation with respect to provincial eligibility criteria for publicly-funded vaccines, such as HPV.

Manitoba Health continues to be committed to providing a safe, effective and cost-effective HPV Immunization Program for the prevention of cervical cancer and dysplasia.

Sincerely,

"Original Signed By"

Richard Baydack, PhD
Communicable Disease Control

"Original Signed By"

Tim Hilderman, MD FRCPC Director,
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Human Papillomavirus (HPV)

Information for Health Professionals

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Table of Contents

Executive Summary 1

Background Information 2

Human Papillomavirus 5

What is Human Papillomavirus (HPV)? 5
How common is HPV? 5
Natural History of HPV Infection 6
Clearance or Persistence of HPV 7
How is Genital HPV Spread? 7
Risk Factors Associated with HPV Infection 8
Genital Warts 8
Cervical Dysplasia and Cancer 8
Non-cervical HPV Infection 9
Distinct Female Populations 10
HPV Infection in Males 10
Distinct Male Populations 11
How Can Someone Reduce Their Risk of Getting HPV? 11
Will Girls/Women Still Need Cervical Cancer Screening? 11

Gardasil®: Summary Product Information 12

Who is Gardasil® Approved in Canada For? 12
Who Should Not Receive Gardasil®? 13
Is Gardasil® Safe? 13
What Are the Common Side Effects of Gardasil®? 13
What Are the Rare Side Effects of Gardasil®? 14
How Long Does Gardasil®Protection Last? 14
Are Additional Doses (Boosters) Required? 14
Two Doses Versus Three Doses of Gardasil® 14
Interrupted Gardasil® Schedules 14
How Effective is Gardasil®? 15

Cervarix™: Summary Product Information 16

Who is Cervarix™ Approved in Canada For? 16
Who Should Not Receive Cervarix™? 16
Is Cervarix™ Safe? 16

What Are the Common Side Effects of Cervarix™? 17
What Are the Rare Side Effects of Cervarix™? 17
How Long Does Cervarix™ Protection Last? 17
Are Additional Doses (Boosters) Required? 17
Two Doses Versus Three Doses of Cervarix™ 17
Interrupted Cervarix™ Schedules 17
How Effective is Cervarix™? 18
Manitoba Health's HPV Immunization Program 19
Who is Eligible for the Vaccine, at No Cost, in Manitoba? 19
Will Manitoba Health Reimburse Individuals Who Pay for the Vaccine? 20
References 21

Executive Summary

The human papillomavirus (HPV) is a virus that can infect many parts of the body, including the genital tract. Approximately 50 different genotypes of HPV can cause genital warts and cancers in the anogenital region, head and neck of both men and women. HPV is estimated to be one of the most common sexually transmitted infections (STIs) in Canada, with most sexually active people having at least one HPV infection in their lifetime.

In 2006, the first HPV vaccine, Gardasil®, was licensed and made available in Canada. When the vaccine is given prior to HPV exposure, it is highly effective in preventing infection from two high-risk genotypes (HPV-16/HPV-18) of HPV, which cause approximately 70 per cent of cervical cancers, and two low-risk (HPV-6/HPV-11) genotypes that are responsible for over 90 per cent of all genital warts.

Although most HPV infections go unnoticed and resolve spontaneously without treatment, some do not and can go on to cause changes in the cells of the cervix (and other anogenital regions of the body) that if left untreated, can develop into cancer. HPV has been shown to be present in over 99 per cent of cervical cancer cases; in Manitoba alone, 53 women were diagnosed with invasive cervical cancer and 20 women died in 2009.

The HPV vaccine (Gardasil®) reduces a woman's risk of getting HPV by approximately 90 per cent. Through Manitoba Health's HPV Immunization Program, Gardasil® is provincially funded for all girls in Grade 6 and for girls/women between the ages of nine and 26 who are at increased risk of HPV infection. Immunization combined with regular Pap test screening are the best ways to reduce a woman's risk of developing cervical cancer.

Background Information

- In July 2006, the regulator for vaccines in Canada, the Biologics and Genetic Therapies Directorate (BGTD) approved for license Merck's Gardasil® Human Papillomavirus (HPV) vaccine,[1] the first vaccine on the Canadian market to offer protection against HPV.
- In February 2007, the National Advisory Committee on Immunization[2,3] (NACI) issued recommendations for the use of Gardasil® for females aged nine to 26. Thereafter, the Chief Public Health Officer of the Public Health Agency of Canada (PHAC) reviewed the 2007 recommendations and strongly supported the HPV vaccine.[3]
- In the spring of 2007, the Canadian Government announced funding to the provinces and territories of $300 million to support a national program for the HPV vaccine. The vaccine was to be publicly-funded for Canadian residents, including First Nations and Inuit residents, both on and off reserve. Shortly thereafter, the Manitoba Minister of Healthy Living at the time committed to providing a publicly-funded HPV Immunization Program.
- In December 2007, the Canadian Immunization Committee (CIC) released the following recommendations relating to the implementation of a HPV immunization program:
  - To reduce by 60 per cent the Cervical Intraepithelial Neoplasia (CIN) 2/3 caused by HPV 16/18 in Canada within 20 years of introduction of a HPV immunization program;
  - To decrease the morbidity and mortality of cervical cancer, its precursors and other HPV-related cancers in women in Canada through combined primary prevention (immunization) and secondary prevention (screening) programs;
  - To implement a school-based HPV immunization program of one female cohort in all Canadian provinces and territories; and,
  - To immunize girls/women for cervical cancer prevention *only* at this time.
- Routine HPV immunization programs for the prevention of cervical cancer had already been implemented in a number of industrialized countries including the United States, Australia and western European countries. These programs primarily targeted females prior to adolescence (nine to 17 years of age) and before onset of sexual activity.
- Both the NACI and the CIC deemed that there was sufficient evidence to support the implementation of routine HPV immunization programs in Canada as part of cervical cancer prevention programs, while recognizing that there were important research questions that needed to be further addressed after implementation. Both committees, however, stressed that the introduction of HPV immunization programs in Canada should not replace the need for fully implemented, organized cervical cancer screening programs combined with education and promotion about safe sex practices.
- From September 2007 to June 2008, Communicable Diseases Control (CDC), Public Health Division, Manitoba Health and Healthy Living convened two groups, the *Human Papillomavirus Immunization Program (HPVIP) Advisory Group* and the *HPVIP Working Group* to identify the issues related to the HPV immunization program in Manitoba and to

offer recommendations on the implementation of the HPV immunization program to the Chief Medical Officer of Health, and then subsequently to the Minister of Healthy Living.

- In March 2008, the HPVIP Advisory Group and HPVIP Working Group made the following recommendations to the Manitoba Minister of Healthy Living:
  - One cohort, Grade 6 females only, to commence in the 2008/09 school year, a three-dose vaccine schedule administered by public health nurses, in the school setting.
- The recommendation was based on the following factors which were consistent with CIC's recommendations:
  - Maximum vaccine effectiveness is achieved when girls are immunized prior to the onset of sexual activity.
  - Public health nurses currently provide publicly-funded immunization programs in school settings (e.g., hepatitis B in Grade 4 and tetanus, diphtheria and pertussis (Tdap) in Grade 8/9).
  - Immunizing females in a school setting is a cost-effective approach.
  - Information on reproductive health is introduced in the Manitoba Education Grade Five Curriculum.
  - School attendance is better in middle years than in senior years therefore supporting the completion of the HPV vaccine series.
- On May 1, 2008, the Manitoba Minister of Healthy Living formally announced the introduction of the HPV Immunization Program for Grade 6 girls, along with other important cervical cancer reduction initiatives including building on provincial public awareness programs for the Manitoba CervixCheck Program (formally known as the Manitoba Cervical Cancer Screening Program) and funding the International Centre for Infectious Diseases (ICID) to undertake research on cervical cancer immunization programs in Canada.
- Since 2008, Manitoba Health and CancerCare Manitoba have been jointly evaluating the province's HPV Immunization Program. The comprehensive evaluation includes examining and reporting on: (1) vaccine uptake in Manitoba; (2) vaccine uptake in First Nations peoples; (3) impact of the vaccine on cervical cancer screening behavior; (4) impact of the vaccine on genital warts; (5) impact of the vaccine on cervical abnormalities; and, (6) vaccine safety. The following major findings are from reports one (1) through three (3):
  - HPV prevalence in Manitoba was determined to be 19%, consistent with the prevalence rate reported in other jurisdictions, with HPV-16 being the most prevalent high-risk genotype.
  - The most consistent risk factors for HPV infection include age of sexual debut, Aboriginal ancestry, lifetime number of sexual partners and number of sexual partners in the previous year.
  - Immunization rates among First Nations girls/women are substantially lower than non-First Nations girls/women.
  - Immunized females are more likely to be screened than non-immunized females.

- In February 2010, BGTD authorized Merck to expand its indications for Gardasil® to include males between nine and 26 years of age. Shortly thereafter, the regulator also approved Cervarix™ (GlaxoSmithKline - GSK), a bivalent HPV vaccine, for use in females 10 to 25 years of age.
- In April 2011, Gardasil® was approved for use in women up to 45 years of age.
- In January 2012, NACI released an updated statement on HPV with the following new recommendations:[8]
  - HPV vaccine (Gardasil®) may be administered to females between 26 and 45 years of age. These females would still benefit from the HPV vaccine even if they are sexually active and/or have had previous pap abnormalities including cervical cancer or genital warts because they are unlikely to be infected with all HPV genotypes contained in the vaccines.
  - HPV vaccine (Gardasil®) in males between nine and 26 years of age for the prevention of some male cancers, anal cancer and genital warts. (Cervarix™ is **NOT** recommended for males at this time).
  - HPV vaccine (Gardasil®) in males who have sex with males (MSM) between nine and 26 years of age. Compared to the general population, MSM have a disproportionately high burden of HPV infection, particularly vaccine-preventable high-risk genotypes 16 and 18.
- CIC is updating its 2007 recommendations; a preliminary 2012 statement suggests that it is not cost-effective to publicly-fund male immunization at this time. Rather, it is more cost-effective to improve immunization rates in the eligible female cohort(s) and/or to increase coverage rates in the overall female population.
- In April 2012, Manitoba Health co-developed with CancerCare Manitoba the *Integrated HPV Committee*, with wide representation from a number of sectors, to guide the development of a provincial HPV strategy to accommodate and integrate the following programmatic components: immunization, screening, laboratory infrastructure, surveillance and research.
- In November 2012, the Public Health Branch of Manitoba Health expanded its eligibility criteria for publicly-funded HPV vaccine to include:
  - Females nine to ≤ 26 years of age with increased risk of HPV infection, as determined by a health care provider. Risk factors can include:
    - Early onset of sexual activity
    - Multiple sexual partners
    - A previous sexually transmitted infection (STI)
    - Adolescent pregnancy
    - An immune system weakened by disease or medical treatment
    - Previous abnormal pap tests
    - Family history of HPV-associated cancers
  - The Province is also targeting and promoting the HPV vaccine to all females who missed the vaccine in Grade 6.

Human Papillomavirus

What is Human Papillomavirus (HPV)?

- There are over 100 genotypes of HPV that can infect many parts of the body.
- Approximately 50 genotypes can infect the genital tract and can cause warts or other illnesses such as cancer (e.g. cervical, penile, anal) in the anogenital region of women and men. HPV can also cause head and neck cancers in both men and women.
- The genotypes of HPV that infect the anogenital area are not the same as the ones that infect other areas of the body such as the fingers, hands and face.
- The various genotypes of HPV are often classified into *low* and *high* risk according to their association with cancer. The "low-risk" genotypes are rarely associated with cancer whereas the "high- risk" genotypes are more likely to lead to the development of cancer.[3]
- High-risk (oncogenic or cancer associated) genotypes include: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 and 82.
  - Possible high-risk genotypes include: 26, 30, 34, 53, 66, 67, 69, 70, 73, 82, 85 and 97.
  - Genotypes 16 and 18 are present in 70% of cervical cancers in North America and in many other parts of the world.[4]
  - Genotype 16 is the most common genotype associated with HPV-positive cancers of the oropharynx and oral cavity.[8]
- Low-risk (non-oncogenic) genotypes include: 6, 11, 40, 42, 43, 44, 54, 61, 72, 73 and 81.
  - Genotypes 6 and 11 cause approximately 90% of anogential warts. However, the genotypes which cause anogenital warts do not usually cause cancer.

How Common is HPV?

- HPV is not a reportable disease in Canada. Therefore, estimates of HPV infection and associated disease burden are based on Canadian prevalence and incidence studies in select populations, such as patients in routine cervical screening clinics, family planning clinics, STI/HIV clinics and university health clinics as well as in the general population.[2]
  - Incidence refers to the number of newly diagnosed cases during a specified period of time, whereas prevalence describes the total number (or percent) of people with a given condition alive on a certain date in a population. The difference between the two measures is that prevalence includes new (i.e. incidence) **and** pre-existing cases and is therefore, a function of new cases, past cases, survival and death.[16]
- The largest Canadian population-based sample to date of 4,821 British Columbia women aged 13 to 86 years found that overall HPV prevalence is 16.8%. The prevalence of HPV genotypes 6, 11, 16 and 18 (the genotypes that are vaccine preventable) were 4.0%, 0.2%, 10.7% and 3.5%, respectively.[8,9]

- The risk of acquiring an HPV infection occurs shortly after the onset of sexual activity[4] with the peak risk of HPV infection occurring within the first five to 10 years of first sexual experience.[8] The peak incidence of HPV occurs in women under 25 years of age.[13]
- Approximately 20% of 15-year-old Canadians have had a sexual encounter.[4]
- The prevalence of HPV infection rises rapidly after the onset of sexual activity and then declines with age.
- High and low-risk genotypes of HPV are the most prevalent in women under 20 years of age.[8]
- The prevalence of genital HPV infections increases with increasing numbers of sexual partners; a clinical study of women who have had more than one sexual partner showed that 46% had cervical HPV infection at three (3) years after their first intercourse.[5]
- HPV infection is so common that most women are likely to be in contact with one or more of the genotypes of this virus at some point in their lives.[4]
  - It is estimated that 75% (3 out of 4) of sexually active Canadians will have at least one HPV infection in their lifetime.
  - In a multi-year study of Aboriginal women in Nunavik, northern Quebec, infections with any genotype and high-risk HPV genotypes were detected in 29.1% and 20.2% of women, respectively. The most common HPV genotype was HPV-16 infections with HPV-16 and HPV-18 accounting for 23.8% of all infections. HPV prevalence in this population was found to be similar to that observed among female university students in Montreal and health clinic attendees in Winnipeg and Nunavut.[2]

Natural History of HPV Infection[5]

*For detailed information, refer to the **Canadian Consensus Guidelines on Human Papillomavirus**, in the *Journal of Obstetrics and Gynecology Canada*, 2007:29(8, supplement 3):S1-S56.

- The virus enters the epithelium, usually through a break in the skin, and then infects the cells.
- The time from infection to release of virus is approximately three (3) weeks. However, the period between infection and appearance of lesions can be weeks to months.
- Most infections are unnoticed and resolve spontaneously within 24 months.
- There is essentially no inflammatory response, which permits immune evasion in the early stages of infection.
- People with compromised immune systems (due to HIV, for example) have higher rates of HPV infection and are more likely to manifest large, multifocal and dysplastic lesions.
- Drugs (steroids), diseases (such as diabetes, renal failure and HIV infection) and cigarette smoking compromise the immune system and may intensify the problem.
- Herpes simplex and bacterial vaginosis may facilitate cutaneous and mucosal entry of the virus.

- Genital HPV lesions include benign genital warts and cervical, vaginal, anal and vulvar cancers.
- Persistent infection with HPV 16 or 18, although infrequent, may lead to cervical dysplasia (i.e. abnormal changes in the cells of the cervix that may develop into cancer if not treated) and cancer.
- Almost all cervical and vaginal cancers and a large proportion of vulvar, anal and oral cancers are associated with high-risk, oncogenic strains of HPV.
- Low-risk HPV genotypes cause genital warts, rarely recurrent respiratory papillomatosis (RRP – characterized by recurrent warts or papillomas in the upper respiratory tract) and oral or conjunctival papillomas.
- HPV infection is difficult to prevent in sexually active adults; preventing transmission is much more difficult to achieve with HPV infection than with other STIs.
- Immunization may be the best primary prevention method as condoms have limited efficacy because HPV can infect areas that are not covered by a condom, and abstinence is unacceptable to many.
- Pap testing is an effective secondary prevention and screening method; with appropriate care and follow-up, most cervical cancers can be detected at an early stage and treated successfully.

Clearance or Persistence of HPV

- Over 90% of HPV infections appear to clear on their own within 2 years.[13]
- The time required for clearance appears to vary with different HPV genotypes, ranging from five to six months for low-risk genotypes and eight to 14 months for high-risk genotypes.
  - Clearance of HPV was determined by an inability for sampling to detect HPV infections. It is unclear whether the virus is completely eliminated or whether it remains latent in basal cells and can reactivate under immune-permissive conditions.[4]

How is Genital HPV Spread?

- Any person who has intimate contact with a person who has one or more HPV genotypes can get the virus. Using condoms may lower the risk of getting HPV and developing HPV-related diseases (e.g. genital warts, genital tract cancers).
- Intimate contact includes skin-to-skin contact with the vagina, vulva, penis, scrotum, anus and/or mouth of a person.
- Co-infection with more than one genotype has been seen, and prior infection with one genotype of HPV does not appear to confer protection against other genotypes. People who are infected with HPV but have no signs or symptoms of infection can transmit HPV as effectively as those with visible lesions (e.g. genital warts).[12]
- HPV can also be passed from mothers to infants during the birthing process.[12]

Risk Factors Associated with HPV Infection

- Any person who is sexually active is at risk of getting HPV. Infection is so common that even a first sexual relationship conveys significant risk of HPV infection.[12] The following factors can put a person at increased risk of HPV infection:
  - Early onset of sexual activity
  - Multiple sexual partners
  - Previous sexually transmitted infections (specifically Chlamydia)
  - Previous abnormal Pap tests
  - A family history of HPV-associated cancers
  - Adolescent pregnancy
  - An immune system weakened by disease or medical treatment

Genital Warts

- HPV genotypes 6 and 11 are the cause of approximately 90% of genital warts.
- Genital warts usually appear as small bumps or groups of bumps, usually in the genital area, in or around the vagina or anus, on the cervix, and on the penis, scrotum, groin or thigh. Warts can be raised or flat, single or multiple, small or large, and sometimes cauliflower shaped. They may appear within weeks or months after sexual contact with an infected person or, may not appear at all.
- If genital warts are left untreated, they may go away, remain unchanged, or increase in size or number but, will not turn into cancer.
- Manitoba data from 2004 suggests the incidence rate of genital warts is 154/100,000 in men and 120/100,000 in women. The data shows a peak in incidence in 1992 followed by a decline, with rates increasing slightly in more recent years, particularly among males.[9]
- It is estimated that the lifetime risk of getting genital warts exceeds 10% and is highest between the ages of 15 and 34 for both sexes.[1]

Cervical Dysplasia and Cancer

- Often cervical cancer does not have symptoms until it is quite advanced. For this reason, and because of the poor sensitivity of cytology, it is important for women to get screened regularly for cervical cancer.
- The time it takes for HPV infection to progress to invasive cervical cancer varies, with typical progression estimated to take up to ten (10) years or longer. In rare cases, lesions appear to progress rapidly with invasive cancer developing in less than one (1) year.[9]
- Other less common HPV-related cancers, such as cancers of the vulva, vagina, anus and penis, may not have signs or symptoms until they are advanced.
- Persistence of oncogenic HPV viruses is required for the cellular changes associated with cervical dysplasia.

- Pap test screening is designed to detect such changes before progression, which permits ablative and excisional therapy to remove the abnormal cells.
- Canada has low rates of cervical cancer but high rates of pre-invasive disease owing to reasonably effective strategies for Pap test screening.
- The link between HPV and cervical cancer has been solidly shown. Most cases of cervical cancer can be found to be attributable to HPV infection. In a pooled analysis of 1,918 patients with cervical cancer, HPV DNA was detected in 99.7%.[4]
- The most frequent high-risk genotypes detected in cervical cancer, in decreasing order of frequency, were 16, 18, 45, 31, 33, 52, 58 and 35.[5]
- Cervical cancer is the second most common cancer affecting women in the world[9] and after breast cancer, is the most common cancer affecting Canadian women 20 to 44 years of age.[1]
- The lifetime risk of developing cervical cancer among Canadian women is 0.7% (1 in 138), and the lifetime risk of dying from cervical cancer is 0.3% (1 in 384).[15]
- In 2011, it was estimated that 1,300 Canadian women were diagnosed with cervical cancer and approximately 350 women died from the disease.[11]
  - Research suggests that people of lower socio-economic status as well as immigrant and Aboriginal women are under-screened, so the number of diagnoses could be much higher.[6]
- In 2009, 53 Manitoba women were diagnosed with invasive cervical cancer and 20 women died.[7]
- Approximately 1 in 4 women will have an abnormal pap test in her lifetime.[7]
- Between January 1, 2007 and December 31, 2009, 93.7% of women had a negative Pap test result, 5% had a low-grade Pap test result and 1.3% had a high-grade Pap test result.[14]

Non-cervical HPV Infection

- Among non-cervical genital cancer and cancers of the head and neck, the proportions related to HPV infection vary:[5]
  - Cancer of the vulva is rare, with an annual rate of new diagnoses of 0.5 to 1.5/100,000. HPV is associated with 20% to 50% of cases and is more frequent in younger women than in older women.[5]
  - Cancer of the vagina is rare, with an annual rate of new diagnoses of 0.3 to 0.7/100,000; 40% of cases are attributable to HPV.[5]
  - High proportions of anal cancer in both women (95%) and men (83%) are associated with HPV infection.[5]
  - Cancer of the penis is rare, with an annual rate of new diagnoses of 1/100,000; penile cancer represents less than 1% of all male cancers.[5,9]
  - Cancers of the mouth and oropharynx have highly variable incidence rates around the world owing to variations in tobacco and alcohol use.[5] It is estimated that 35.6% of oropharyngeal cancers and 23.5% of oral and 24% of laryngeal cancers are attributable to HPV.[9]

- Recurrent respiratory papillomatosis (RRP) occurs in 4.3/100,000 children and 1.8/100,000 adults in the United States.[5]
- It is estimated that 1 in 400 children born to women with genital infection with HPV genotypes 6 or 11 will have subsequent RRP.[5]

Distinct Female Populations

- HPV can be sexually transmitted between women.
- Recommendations on Pap test screening and immunization should not vary for women who have sex with women.
- HIV-positive women carry HPV at higher rates and have higher rates of cervical dysplasia. The high rates appear to be related to HIV virus load, whereas the association with immune status and HPV persistence is modest.
- Some studies suggest that cervical dysplasia progresses faster to invasive cancer, in direct relation to the degree of immunodeficiency.
- Inuit women of Nunavut have higher rates of cervical cancer than Canadian women in general and in comparison to other provinces and territories.[5]
  - Cervical cancer is the most common cancer of women in this region, representing 35% of all cancers diagnosed.
  - The prevalence of oncogenic HPV in this population is 26% and is inversely related to age.
- Indigenous peoples are disproportionately affected by HPV infections, are at a greater risk for HPV-related cancers, are more likely to be diagnosed at a later stage and are less likely to survive a diagnosis of cervical cancer than people who are non-Indigenous.[9]

HPV Infection in Males

- To date, studies in males are less extensive than in females.
- Prevalence in males, as in females, varies according to the population studied, limiting the generalizability of results to the broader population.
- HPV prevalence among males has been shown to vary by the sex of their sexual partners, the presence of cervical pathology in their female partners and geographic region.
- One study reported a prevalence of any HPV genotype from any site of 69.8%. The population studied was heterosexual males in Vancouver, British Columbia attending a STI clinic.[9]
- In the *HPV in Men (HIM)* study, HPV-16 was the most common oncogenic genotype detected (6.5%), followed by HPV genotype-51 (5.3%) and genotype-59 (5.3%).[9]
- It is estimated that HPV infection in males is associated with 80 to 90 per cent of anal cancers and 40 to 50 per cent of penile cancers.[9]

- Lack of circumcision is a plausible risk factor for HPV infection. A recent randomized-controlled trial found that high-risk HPV was identified in 14.8% of circumcised men and 22.3% of uncircumcised men.[8]

Distinct Male Populations[9]

- HPV can be sexually transmitted between men.
- HPV infection is highly prevalent in men who have sex with men (MSM).
- HIV-positive men carry HPV at higher rates; the *San Francisco Men's Health* study found that anal HPV DNA was detected in 93% of HIV-positive and 61% of HIV-negative MSM.
- Rates of anal cancer among HIV-positive MSM exceed the cervical cancer rate among women, even in areas of the world with the highest rates of cervical cancer.
- Despite the limitations in determining HPV infection status in males, symptomatic and asymptomatic HPV infections appear to be common.

How Can Someone Reduce Their Risk of Getting HPV?

- The only way to completely avoid HPV infection is to not have intimate contact (skin-to-skin contact with the vagina, vulva, penis, scrotum, anus or mouth) with infected individuals.
- For those who choose to be sexually active, condoms may lower the risk of getting HPV and other sexually transmitted infections, if used correctly all the time, for every sex act from start to finish. However, HPV can infect areas that are not covered by a condom; therefore, condoms may not fully protect against HPV.
- Abstinence is the best way to prevent HPV infection.
- Once sexually active, consideration should be given to choosing one long-term sexual partner, or limiting the number of sexual partners.
- It is also important to give consideration to partners' sexual histories (e.g. if they have had a previous partner), as they may not know they are infected with HPV.

Will Girls/Women Still Need Cervical Cancer Screening?

- It is very important that girls/women who have been immunized against HPV continue to have regular Pap tests as the vaccine does not protect against all genotypes of HPV.
- Even when someone is immunized, it is still possible to become infected with one of the less common genotypes of HPV not covered by the vaccine.

For more information, visit **CervixCheck, CancerCare Manitoba** at: http://telleverywoman.ca/

Gardasil®: Summary Product Information

- Since the launch of the HPV Immunization Program in 2008, Manitoba Health has recommended and publicly-funded the Gardasil® vaccine for girls in Grade 6.
- Gardasil® is a recombinant, quadrivalent vaccine that offers protection against two high-risk genotypes of HPV (16 and 18), which cause approximately 70 per cent of cervical cancers, and two low-risk genotypes of HPV (6 and 11), which cause approximately 90 per cent of all genital warts.
- Gardasil® is thought to be most effective before the onset of sexual activity; however, females between the ages of nine and 45 and males between nine and 26 can still receive the vaccine even if they have already been sexually active.
  - People who are already sexually active can still benefit from Gardasil® because they are unlikely to be infected with all four (4) HPV genotypes contained in the vaccine.
- It is very important the entire vaccine series be administered to receive the maximum benefits from the vaccine.
- People cannot get HPV from the vaccine as it does not contain a live virus.

The vaccine does not treat existing HPV infections, genital warts or cervical abnormalities.

Who is Gardasil® Approved in Canada For[1]?

- Girls/women nine through 45 years of age for the prevention of infection caused by the HPV genotypes 6, 11, 16 and 18 and the following diseases associated with the HPV genotypes included in the vaccine:
  - Cervical, vulvar, and vaginal cancer caused by HPV genotypes 16 and 18; and,
  - Genital warts (condyloma acuminata) caused by HPV genotypes 6 and 11.
- And the following precancerous/dysplastic lesions caused by HPV genotypes 6, 11, 16 and 18:
  - Cervical adenocarcinoma *in situ* (AIS);
  - Cervical intraepithelial neoplasia (CIN) grade 2 and grade 3;
  - Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3;
  - Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3; and,
  - Cervical intraepithelial neoplasia (CIN) grade 1.
- Girls/women nine through 26 years of age for the prevention of:
  - Anal cancer caused by HPV genotypes 16 and 18; and,
  - Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3 caused by HPV genotypes 6, 11, 16 and 18.
- Boys/men nine through 26 years of age for the prevention of infection caused by HPV genotypes 6, 11, 16 and 18 and the following diseases associated with the HPV genotypes included in the vaccine:

  - Anal cancer caused by HPV genotypes16 and 18;
  - Genital warts (condyloma acuminata) caused by HPV genotypes 6 and 11; and,
  - Anal intraepithelial neoplasia (AIN) grades 1, 2 and 3 caused by HPV genotypes 6, 11, 16 and 18.

Who Should Not Receive Gardasil®?

- Females under the age of nine or over the age of 45.
- Males under the age of nine and over the age of 26.
- Pregnant women.
- Patients who are hypersensitive to the active substances or to any of the ingredients of the vaccine.
  - The product does not contain a preservative (Thimerosal) or antibiotics.
- Individuals who develop symptoms indicative of hypersensitivity after receiving a dose of Gardasil® should consult their doctor, public health nurse or nurse practitioner prior to receiving further doses of Gardasil®.

Is Gardasil® Safe?

- Yes, Gardasil® is considered safe. As with all vaccines, adverse events may occur.
- Health Canada conducted a scientific review of the quality, safety and effectiveness of Gardasil® and approved it for use before the Province recommended and publicly-funded it.
- Once a vaccine is approved and in use, Health Canada and the Public Health Agency of Canada (PHAC) continue to monitor its use.
- The PHAC coordinates and supports the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS), which collects reports from health care providers on adverse events following immunization.
- Canada also has an active surveillance system that is based out of 12 pediatric hospitals across Canada, called IMPACT (Immunization Monitoring Program ACTive). In addition, an expert scientific committee in Canada called the Advisory Committee on Causality Assessment (ACCA) assesses select reports and determines whether or not the vaccine was likely to have caused the reaction.

In the event of an adverse event, please complete the *Adverse Event Following Immunization Reporting* form, available online at: www.gov.mb.ca/health/publichealth/cdc/div/info.html.

What Are the Common Side Effects of Gardasil®?

- The most commonly reported side effects are:
  - Pain, swelling, itching and redness at the injection site.
  - Fever, nausea, dizziness, headache and vomiting.
  - Fainting has been reported (and may occur) following immunization in the adolescent population.
- See the most recent product monograph for other common side effects.

What Are the Rare Side Effects of Gardasil®?

- As with any vaccine or drug, severe, allergic, life-threatening (anaphylactic) reactions may occur with symptoms such as:
  - Difficulty breathing
  - Wheezing (bronchospasm)
  - Hives or rash
- As with other vaccines, side effects that have been observed after immunization include:
  - Swollen glands (neck, armpit, or groin).
  - Guillain-Barré Syndrome (GBS), a rare form of paralysis that is usually temporary, has been reported but a confirmed link to the vaccine has not been established.
- See the most recent product monograph for other rarely reported side effects.

How Long Does Gardasil® Protection Last?

- Recent studies have indicated good protection against HPV for at least five (5) years of follow-up.

Are Additional Doses (Boosters) Required?

- Additional booster doses are not recommended at this time; future recommendations will be based on scientific evidence.

Two Doses versus Three Doses of Gardasil®

- Based on current evidence, NACI recommends providing three doses of Gardasil®.
- Further study on the effectiveness of a two-dose HPV vaccine schedule is required. As data from ongoing research becomes available, recommendations will be updated accordingly.

Interrupted Gardasil® Schedules

- If the Gardasil® vaccine schedule is interrupted, the vaccine series does not need to be restarted.
- If the series is interrupted after the first dose, the second dose should be given *at least one month after the first dose*, and the second and third doses should be separated by an interval of at least 12 weeks.
- If only the third dose is delayed, it should be administered as soon as possible.
- Individuals who have accessed the immunization program in other provinces but have not completed the series are advised to contact their nearest Public Health Office to consult with a Public Health Nurse. The nurse will review the vaccine schedule for completion of the series and eligibility in accordance with Manitoba's publicly funded program.

How Effective is Gardasil®?

- HPV immunization with Gardasil® has been shown to be highly immunogenic and is very efficacious in preventing persistent HPV infection in women not previously infected with the HPV genotypes used in the vaccine.[5]
- When injected intramuscularly, Gardasil® induces immunity without actual infection.
- Clinical trials involving monovalent, bivalent, and quadrivalent vaccines have shown over 90% protection against persistent HPV infection and related cervical dysplasia due to the vaccine subtypes in young, healthy females who have not begun sexual activity.
- Trials have also shown more than 90% efficacy in preventing incident and persistent HPV infection in both women and men.
  - After 5 years of enrollment of a study population, there was 96% protection against persistent HPV infection, and there were no cases of CIN related to HPV 16 or 18 or genital warts related to HPV 6 or 11.
  - After 3.6 years, immunization with Gardasil® resulted in an overall reduction in abnormal Pap tests of 17%, irrespective of HPV genotype.[8]
- Among women previously treated for cervical disease, immunization with Gardasil® was associated with a reduction in the incidence of new CIN2+ disease due to any HPV genotype of 65% and of genital warts, VIN or VaIN due to any HPV genotype of 47%.[8]
- Antibody response has been excellent in the immunized females and much greater than with natural infection.
  - At the end of follow-up, the vaccine-induced antibody titres were 17 and 14 times higher than the titres induced by naturally occurring infection with HPV genotypes 16 and 18, respectively.
  - After 36 months, 94% remained seropositive for antibodies for HPV genotype 6, 96% for genotype 11, and 100% for genotype 16. However, only 76% remained seropositive for antibodies for genotype 18. The significance of antibody levels and seropositivity is unknown at this time.[2]
- Clinical trials suggest there is some cross-protection afforded by Gardasil®, specifically against non-vaccine HPV genotypes 31, 33 and 45. However, the clinical significance of this cross protection is unknown.[9]
  - After 3.6 years of follow-up, immunization with Gardasil® of generally HPV-naïve women between 16 and 26 years of age resulted in a significant reduction in the incidence of HPV genotypes 31 and 45 (two of the most common genotypes after HPV-16/HPV-18) by 40%.[8]

For more information about Gardasil® (e.g., administration, storage, dosage, etc.), see the Product Monograph at: www.merckfrosst.ca/assets/en/pdf/products/GARDASIL-PM_E.pdf

Cervarix™: Summary Product Information

- The Cervarix™ vaccine is **not** included under Manitoba Health's HPV Immunization Program at this time.
- Cervarix™ (GlaxoSmithKline - GSK) is a recombinant, adjuvanted vaccine that offers protection against two high-risk genotypes of HPV (HPV-16/HPV-18), which cause approximately 70 per cent of cervical cancers.
  - Cervarix™ does **not** protect against the two low-risk genotpyes (HPV-6/HPV-11) that are responsible for 90% of genital warts. Therefore if wart protection is desired, Gardasil® should be used.
- Cervarix™ is thought to be most effective before the onset of sexual activity; however, females nine to 25 years of age can still receive Cervarix™ even if they have already been sexually active.
  - Cervarix™ is not approved for use in males of any age at this time.
- It is very important the entire vaccine series be administered to receive the maximum benefits from Cervarix™.
- Girls/women cannot get HPV from Cervarix™ as the vaccine does not contain a live virus.

Who is Cervarix™ Approved in Canada For?

- Females from nine to 25 years of age for the prevention of cervical cancer (squamous cell cancer and adenocarcinoma) by protecting against the following precancerous or dysplastic lesions caused by oncogenic HPV genotypes 16 and 18:
  - Cervical intraepithelial neoplasia (CIN) grade 2 and grade 3;
  - Cervical adenocarcinoma *in situ* (AIS); and,
  - Cervical intraepithelial neoplasia (CIN) grade 1.

Who Should Not Receive Cervarix™?

- Females under the age of nine or over the age of 25.
- Males of any age.
- Pregnant women. Women should avoid pregnancy for two months following Cervarix™ immunization.
- Females who are hypersensitive to any components of the vaccine.

Is Cervarix™ Safe?

- Yes, Cervarix™ is considered safe. As with all vaccines, adverse events may occur.
- Health Canada conducted a scientific review of the quality, safety and effectiveness of the vaccine and approved it for use before it became available in Canada.

In the event of an adverse event, please complete the *Adverse Event Following Immunization Reporting* form, available on at: www.gov.mb.ca/health/publichealth/cdc/div/info.html.

What Are the Common Side Effects of Cervarix™?

- The most commonly reported side effects are:
  - Pain, swelling, itching, and redness at the injection site.
  - Fever, nausea, dizziness, headache and vomiting.
- See the most recent product monograph for other common side effects.

What Are the Rare Side Effects of Cervarix™?

- As with any vaccine or drug, severe, allergic, life-threatening (anaphylactic) reactions may occur with symptoms such as:
  - Difficulty breathing
  - Wheezing (bronchospasm)
  - Hives or rash
- See the most recent product monograph for other rarely reported side effects.

How Long Does Cervarix™ Protection Last?

- Recent studies have indicated good protection against HPV for at least seven (7) years of follow-up.

Are Additional Doses (Boosters) Required?

- Additional booster doses are not recommended at this time; future recommendations will be based on scientific evidence.

Two Doses Versus Three Doses of Cervarix™

- Based on current evidence, NACI recommends providing three doses of the Cervarix™ vaccine.
- Further study on the effectiveness of a two-dose HPV vaccine schedule is required. As data from ongoing research becomes available, recommendations will be updated accordingly.

Interrupted Cervarix™ Schedules

- If the Cervarix™ vaccine schedule is interrupted, the vaccine series does not need to be restarted.
- If the series is interrupted after the first dose, the second dose should be given *at least one month after the first dose*, and the second and third doses should be separated by an interval of at least 12 weeks.
- If only the third dose is delayed, it should be administered as soon as possible.
- Individuals who have accessed the immunization program in other provinces but have not completed the series are advised to contact their nearest Public Health Office to consult with a Public Health Nurse. The nurse will review the vaccine schedule for completion of the series and eligibility in accordance with Manitoba's publicly funded program.

How Effective is Cervarix™?

- HPV immunization with Cervarix™ has been shown to be highly immunogenic and is very efficacious in preventing persistent HPV infection in women not previously infected with the HPV genotypes used in the vaccine.
- Three (3) doses of Cervarix™, like Gardasil®, are ineffective at clearing infections from HPV genotypes 16 and 18. However, immunization with Cervarix™ in women previously treated for cervical disease was associated with a reduction in the incidence of new CIN2+ disease due to any HPV genotype of 88.2%.[8]
- Trials have shown more than 95% efficacy in preventing incident and persistent HPV infection.
  - At 6.4 years of follow-up, there was 100% protection against persistent HPV infection, and there were no cases of CIN related to HPV 16 or 18.[8]
- Antibody response has been excellent in the immunized females and much greater than with natural infection.
  - After 36 months, 94% remained seropositive for antibodies for HPV genotype 16 and 91% for HPV genotype 18.[8]
- Clinical trials suggest there is some cross-protection afforded by the Cervarix™ vaccine. To date, the research is showing that Cervarix™ produces higher vaccine efficacy against non-vaccine HPV genotypes 31, 33 and 45 than Gardasil®,[9] however, the clinical significance of this cross protection is unknown.[8]
  - Cervarix™ was 100% effective in preventing two (2) of the most common non-vaccine containing oncogenic genotypes (31 and 45); 68.2% for the five (5) most common non-vaccine-containing oncogenic HPV genotypes (31, 33, 45, 52 and 58); and, 66.1% for the ten (10) most common non-vaccine containing oncogenic HPV genotypes (31, 33, 35, 39, 45, 51, 52, 56, 58 and 59).[8]

For more information about Cervarix™ (e.g., administration, storage, dosage, etc.), see the Product Monograph at: http://www.gsk.ca/english/docs-pdf/product-monographs/Cervarix.pdf

Manitoba Health's HPV Immunization Program

Who is Eligible for the HPV Vaccine, at No Cost, in Manitoba?

- Since September 2008, all females in Grade 6 were offered and will continue to be offered the HPV vaccine free-of-charge as part of their routine childhood immunizations.
- Once eligible, the individual may receive the HPV vaccine at a later time (as with other vaccine eligibility criteria in Manitoba) at no additional cost. This includes all females previously unimmunized against HPV who were born on or after January 1, 1997.
- Starting November 2012, all females 9 to ≤ 26 years of age with increased risk of HPV infection, as determined by a health care provider, are eligible to receive the HPV vaccine free-of-charge. Factors associated with increased risk can include:
  - Early onset of sexual activity
  - Multiple sexual partners
  - A previous sexually transmitted infection (STI)
  - Adolescent pregnancy
  - An immune system weakened by disease or medical treatment
  - Previous abnormal Pap tests
  - Family history of HPV-associated cancers
- To receive the vaccine outside of the Grade 6 school program, arrangements can be made with the local public health office, nursing station or doctor's office.
- Although Gardasil® is approved for use in males between 9 and 26 years of age, immunizing boys/men against HPV is not currently part of Manitoba Health's HPV Immunization Program and is therefore not provincially funded at this time.
  - Manitoba Health is conducting a thorough review of the existing evidence; as data from ongoing research becomes available, the provincial HPV Immunization Program will be updated accordingly, pending funding and product availability.
- Immunization in Manitoba is voluntary; the person being immunized or the parent/guardian of the child being immunized must provide explicit consent (written or verbal) prior to immunization.
- Individuals who do not meet Manitoba Health's vaccine eligibility criteria can contact their doctor or nurse practitioner who will discuss their individual care and provide a prescription (out-of-pocket expense) to be filled at a pharmacy; the cost of the vaccine series may vary by pharmacy.
- If an individual requests the vaccine and is receiving financial assistance from Employment and Income Assistance (EIA), refer the individual to the EIA case coordinator in their area.

Will Manitoba Health Reimburse Individuals Who Pay for the Vaccine?

- No, as per Manitoba Health's Policy on Eligibility for Publicly-Funded Vaccines, which is summarized at: http://www.gov.mb.ca/health/publichealth/cdc/vaccineeligibility.html
- If an individual has third party private health insurance, refer the individual to their provider regarding financial reimbursement.
- Manitoba Health's Pharmacare program does not cover the cost of this vaccine.

For more information on **Manitoba Health's HPV Immunization Program**, see the Public Health website at: http://www.gov.mb.ca/health/publichealth/index.html.

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