HPV AND PREVENTION

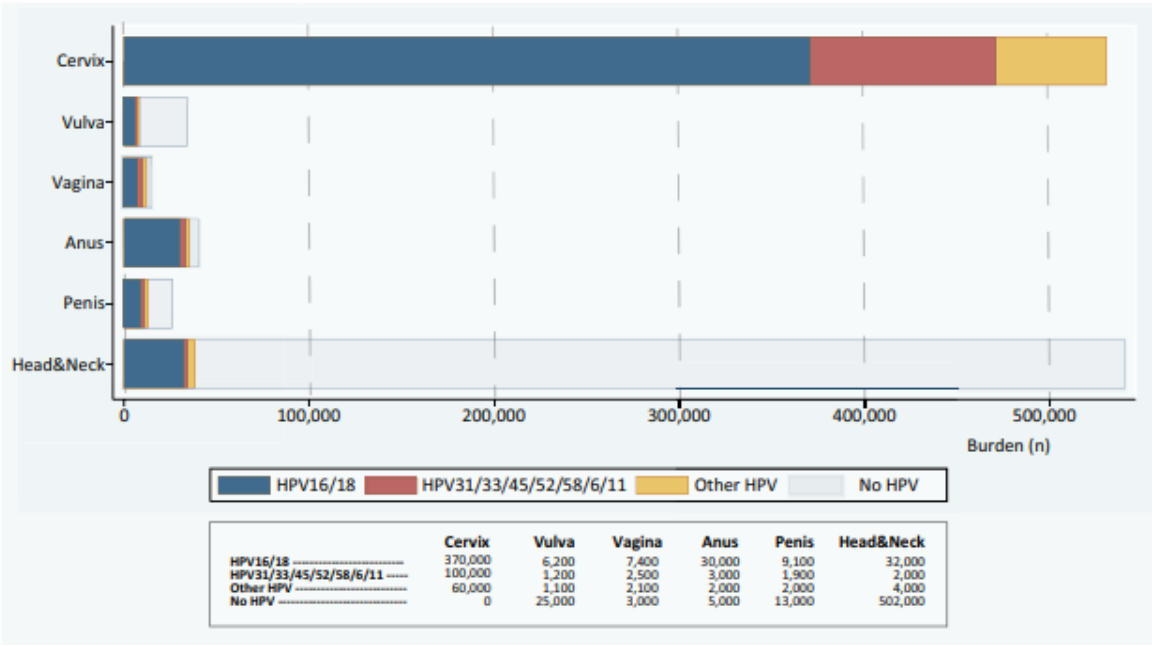
Key Messages:

- HPV is responsible for most cervical cancers as well as many anogenital and oropharyngeal cancers.
- HPV vaccination can prevent up to 90-100% of HPV infections. The HPV vaccine is available to all CAF members (CFHS Instr 6636-63).
- Cervical cancer screening is still recommended even if vaccinated against HPV.

The Human Papilloma Virus (HPV) is responsible for several cancers

Human Papillomavirus (HPV) infections are the most common sexually transmitted infections. There are over 200 strains of HPV, and they are broadly classified into high- and low-risk types. About 75% of Canadians that are sexually active will have at least one HPV infection in their lifetime without vaccination.[i] [ii] Most HPV infections occur without symptoms and self-resolve without treatment.[iii] However, persistent infection with a high-risk HPV type can lead to cervical and anogenital cancers, as well as certain head and neck (oropharyngeal) cancers if not cleared.

Figure 1. Worldwide-distribution of HPV types and their prevalence in HPV-related cancers.[iv]



	Cervix	Vulva	Vagina	Anus	Penis	Head&Neck
HPV16/18	370,000	6,200	7,400	30,000	9,100	32,000
HPV31/33/45/52/58/6/11	100,000	1,200	2,500	3,000	1,900	2,000
Other HPV	60,000	1,100	2,100	2,000	2,000	4,000
No HPV	0	25,000	3,000	5,000	13,000	502,000

Incidence of cancers of the oropharynx has increased. Up to 70% of new oropharyngeal cases are attributed to HPV in North America and Western Europe.[v] These HPV-related head and neck cancers also appear to occur in men more often than women.[vi]

The global burden of HPV-related cancers in adults is estimated at about 5.2% of all cancers, with cervical cancer the third most common cancer and fourth leading cause of death in females.[vii]

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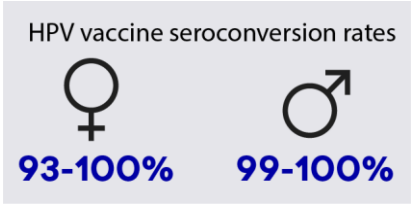
HPV vaccines are safe and well-studied

HPV vaccines are safe and well-tolerated. More than 250 million doses of HPV vaccines have been administered since 2007. Clinical trials have not found a direct link to HPV vaccination and serious adverse events.[viii] The most common side effects are injection-site pain, swelling, and erythema, which are mild and common reactions to immunization.[ix]

Contraindications to this vaccine include a history of an allergic reaction to a previous dose of any HPV vaccine, or to any component of the vaccine or its container.[x] Potential allergens in the 9vHPV (Gardasil®9) vaccine include polysorbate 80 and yeast protein.[xi]

HPV vaccine is highly immunogenic and can decrease the risk of cancers

HPV vaccines are prophylactic and can prevent up to 90-100% of HPV infections if administered prior to exposure.[xii]



The two HPV vaccines available in Canada are recombinant (not live) vaccines: the nonavalent vaccine (9vHPV - Gardasil®9) and the bivalent vaccine (2vHPV, Cervarix®).

The CAF uses the 9vHPV vaccine which provides the most coverage against oncogenic strains (16, 18, 31, 33, 45, 52, and 58) and the two strains that cause anogenital warts (6, 11). The 9vHPV vaccine can prevent 90-100% of HPV infections prior to exposure to the virus. [xiii]

The bivalent 2vHPV vaccine only targets the two highest risk HPV strains (16, 18).[xiv]

All of the HPV vaccines elicit seroconversion rates of 93 to 100 percent in females and 99 to 100 percent in males.[xv] Immunization against HPV types 16 and 18 alone prevents approximately 70% of anogenital and 60% of high-risk precancerous lesions on the cervix.[xvi]

Figure 2. High-risk HPV strains and their role in organ-specific cancers. [xvii]

	Cervix	Vulva	Vagina	Penis	Anus	Head and Neck
1st	HPV16	HPV16	HPV16	HPV16	HPV16	HPV16
2nd	HPV18	HPV33	HPV31	HPV6	HPV18	HPV33
3rd	HPV45	HPV18	HPV18	HPV33	HPV33	HPV35
4th	HPV33	HPV45	HPV33	HPV45, 35	HPV31	HPV18
5th	HPV31	HPV52	HPV45,58	HPV59	HPV58,6	HPV26
6th	HPV52	HPV31,56	HPV52	HPV18,52,11	HPV35	HPV45
7th	HPV58	HPV58,6	HPV51	HPV58	HPV11	HPV52
AF among HPV Positive cancers (%)*	90	88	86	88	95	96+
Total AF(%)**	80	25	64	30	84	12

The attributable fraction (AF) in red refers to the proportion among HPV positive cancers that is attributable to any of the seven listed HPV types. The AF in black** refers to the fraction of total organ-specific cancer attributable to any of the seven listed HPV types.*

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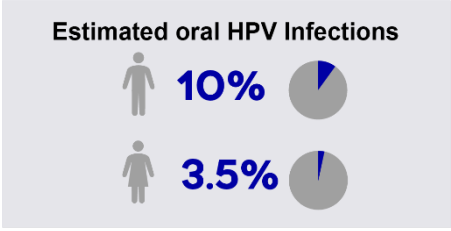
Initial studies on HPV vaccines were powered to look for prevention of cervical lesions and anogenital warts. Since then, it has been found that oncogenic HPV 16, 18, and other high-risk strains play a role in cancers other than cervical: including anal, penile, oropharyngeal, vaginal, and vulvar cancers. We have also learned that the 9vHPV vaccine may play a role in reducing the risk of developing some of these cancers.[xviii]

> A history of an abnormal pap test (i.e. cervical dysplasia), genital warts, or history of HPV infection are NOT contraindications to receiving the HPV vaccine.

Cervical Cancer: A history of an abnormal pap test (i.e. cervical dysplasia), genital warts, or history of HPV infection are NOT contraindications to receiving the HPV vaccine.[xix] In fact, there is some evidence to suggest that HPV vaccination decreases the risk of recurrent cervical dysplasia (reactivation of the virus), including in people who have undergone surgical treatment such as a Loop Electrosurgical Excision Procedure (LEEP).[xxxxi] Moreover, people who have previously been infected with HPV are still at risk of being infected with other HPV strains.

Oropharyngeal Cancer: The 9vHPV vaccine is believed to prevent oropharyngeal cancers, which are a growing concern, particularly in young healthy people. Formerly, oropharyngeal cancers were causally linked to environmental exposures such as smoking and alcohol. As people endorsed healthier behaviors, such as reducing smoking and alcohol consumption, oropharyngeal cancers had been on the decline. However, in recent years there has been a dramatic rise in oropharyngeal cancer related to high-risk HPV types. HPV has been linked to up to 70% of new cases in North America.[xxii] Oropharyngeal cancer is the most common HPV-related cancer in men. It is estimated that 10% of men and 3.5% of women have oral HPV, potentially putting them at risk of developing oropharyngeal cancer. [xxiii]



Research in the United Kingdom has demonstrated the preventive value of the 9vHPV vaccine on oropharyngeal HPV. In a study of 18-to 30-year-olds, there was a 90% risk reduction in oropharyngeal HPV infection in those vaccinated versus those not vaccinated. There was no significant difference in the presence of strains not covered by the vaccine.[xxiv]

The U.S. Food and Drug Administration used their Accelerated Approval process to add the prevention of oropharyngeal and other head and neck cancers caused by HPV to the list of indications for the 9vHPV vaccine. Post-marketing studies are expected to be completed by 2026.[xxv]

All CAF members, at any age, are eligible to receive the HPV vaccine

The indications for the HPV vaccine have continued to broaden. The National Advisory Committee on Immunizations (NACI) recommends HPV vaccination for all age groups represented in the CAF, with a strong recommendation for those ages 9-26 years.[xxvi] However, those 27 years and over remain eligible to receive the vaccine. [xxvii]

As part of the CAF comprehensive immunization program, the first dose of 9vHPV vaccine is now offered during basic training, although some CAF members may decline it or miss it. Many patients may not understand their risk, know their future risk, or identify with risk factors (e.g.

non-monogamy, unknown oropharyngeal colonization in a partner).[1] Given the strong safety profile of this vaccine, the demonstrated potential protection and benefits offered from receiving the HPV vaccine would outweigh the risk in most circumstances. All CAF members should be provided information on the vaccine and should have the opportunity to discuss potential risks with their healthcare provider so they can make an informed decision regarding protection against potential future HPV exposures.[xxviii] [2] [3]

There are new HPV vaccine recommendations published

Previously, a three-dose schedule was recommended if the vaccination series was initiated after the age of 15.[xxix] However, the July 2024 NACI update on HPV vaccination now recommends a two-dose schedule for those ages 21 years and older, separated by at least 24 weeks apart.[xxx] This schedule is for immunocompetent persons only. For persons 9 to 20 years of age, NACI recommends one-dose of HPV vaccine. The evidence for the reduced number of doses is based on studies demonstrating noninferior antibody titers after one dose.[xxxi]

> “HPV vaccination now recommends a two-dose schedule for those ages 21 years and older, separated by at least 24 weeks apart.”

For immunocompromised people, a three-dose schedule is still recommended for all age groups.[xxxii] Re-immunization with the same HPV vaccine (booster) is not indicated at this time, as protection has been shown to last at least 10 years (for the 3-dose and 2-dose series) and long-term data is not yet available. [xxxiii] However, those who have completed the immunization series with a different vaccine (2vHPV or 4vHPV) and are at ongoing risk may benefit from one additional dose of 9vHPV vaccine.[xxxiv]

[1] Additionally, while the highest risk for HPV infection is within 5 to 10 years of sexual debut, a second peak in HPV prevalence is seen in women 45 years and older (Public Health Agency of Canada, 2024).

[2] Since the introduction of publicly funded HPV vaccination school programs in 2007, an increasing number of CAF members have had the opportunity to be vaccinated. However, some CAF members may have missed or declined the HPV vaccine for a variety of reasons.

[3] Studies have shown HPV vaccine hesitant parents resulted in many adolescents not receiving one or more doses of the vaccine. Often these reasons were non-medical, and specific to the HPV vaccine. The proportion of parents who reported one or more reasons that they did not intend to vaccinate their child fell into the following categories: 43.8% vaccine misinformation, 18.0% safety and efficacy concerns, 17.0% lack of knowledge about the vaccine, 16.0% systemic barriers (such as cost, vaccine not available, vaccine not recommended, not a school requirement, no OBGYN, no doctor or doctor’s visit scheduled), 5.5% socio-cultural reasons (such as guardians don’t believe in immunizations, it was a family/parental decision, or decision due to religious practices and beliefs). (Cheruvu, et al. (2017)).

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Table 1: Adapted from the 2024 NACI recommendations on HPV immunization schedules[xxxv]

Group	NACI Recommended Dosing	Minimum interval
9-20 years of age	**1-dose (9vHPV)**	**N/A**
21-26 years of age	2-doses (9vHPV)	24 weeks apart
27 years and older	2-doses (9vHPV)	24 weeks apart
Immunocompromised and/or living with HIV (9 years and older)	3-doses (9vHPV)	1st & 2nd dose: minimum 4 weeks apart 2nd & 3rd dose: minimum 12 weeks apart 1st & 3rd dose: minimum 24 weeks apart

Cigarette smoking and HPV infection have synergistic effects in the development of cervical dysplasia and cancer

Cigarette and nicotine containing e-cigarette smoking: While it is well known that cigarette smoking has impacts on multiple systems throughout the body, smoking nicotine has been associated with increased risk of vaginal tract infections, and particularly HPV infections. There appears to be a synergistic effect of smoking and HPV infection on development of cervical dysplasia and cancer.[xxxvi] In fact, cotinine, the major metabolite of nicotine, has been shown to be concentrated in cervical mucous. Furthermore, nicotine has been implicated in disruption of the vaginal biome which impacts susceptibility of the cells to infections, including HPV infections.[xxxvii] Smoking also plays an important role in persistent HPV infection as mechanical cell damage reduces the ability to clear the HPV virus.[xxxviii] [xxxix]

> “Nicotine has been implicated in disruption of the vaginal biome which impacts susceptibility of the cells to infections, including HPV infections.”

Cannabis: Reported use of cannabis has increased considerably over the last decade. While there is the possibility that increased reporting is related to the changed legal considerations, it is important to consider the impact of cannabis use on the development of HPV-mediated cancers. While this research is still ongoing, there has been a demonstrated site-specific increase in HPV-mediated oropharyngeal cancers associated with increased inhaled cannabis use. This does appear, at least in the pharynx, to be dose-dependent.[xl]

HPV infection and pregnancy

Vertical transmission of HPV to the fetus during pregnancy is rare; however, HPV has been found in amniotic fluid and placental tissue.[xli] While transmission to the fetus can occur, some studies suggest that the infant clears the HPV infection, and therefore, not clinically significant.[xlii] There are some reported adverse outcomes from HPV infection during pregnancy including preterm birth, miscarriage, intrauterine growth restriction and premature rupture of membranes.[xliii] However, a recent systematic review found the data surrounding HPV infection and its impact on pregnancy remains inconclusive and further research is needed in this area.[xliv]

It is important to have conversations on HPV vaccination status as part of family planning. The 2024 NACI guidelines recommends HPV vaccination during pregnancy.[xlv] Some patients may find this concerning, but it is important to have a risk-benefit conversation with them, given the above statements. It would be ideal to update HPV vaccination status prior to pregnancy, as vaccinating during pregnancy may be unacceptable to some patients. Prior to this recommendation, when inadvertent vaccination has occurred during pregnancy, there has been no evidence of harm to the pregnancy or the developing fetus.[xlvi]

HPV and anogenital warts

Anogenital warts (AGW) are common and predominantly caused by HPV 6 and 11 which are low-risk strains that are very rarely oncogenic. External AGW can occur on the vulva, penis, groin, perianal region, anus, in the vagina and in the suprapubic region.[xlvii] Their presentation can vary based on location. Typically, they are raised, flesh-coloured cauliflower-like papules or plaques[xlviii], however, they may appear more flat, particularly in the anal region. Diagnosis is usually clinical (visual inspection), but colposcopy and/or biopsy can be considered in some cases.[xlix]

9vHPV vaccine was
68-77%
effective in preventing AGW in female enrollees after 2 doses.

Vaccines that protect against HPV strains 6 and 11 were found to be highly effective in preventing AGW, particularly in younger populations (16-24 years) and in those not previously exposed to HPV.[l 4] One observational study found that the 9vHPV vaccine was 68 - 77% effective in preventing AGW in female enrollees after 2 doses.[li] Likewise, the quadrivalent vaccine was found to be approximately 66% effective in preventing AGW in the overall population with unknown HPV exposure.[lii] The exact effect of the vaccine in preventing recurrence or in treating active AGW is still unclear, but studies are being conducted and evidence to date suggests that the HPV vaccines may play a role in resolution of AGW.[liii liv lv] The bivalent vaccine (2vHPV) was not designed to prevent wart-causing strains.

Treatment is not always necessary for AGW and is usually for symptom management, wart removal (e.g. removal during pregnancy when AGW may impact delivery), and to minimize transmissibility. AGW have a high viral load and are therefore highly infectious.[lvi] Without treatment, some AGW stay stable or increase in size/number, while approximately 40% spontaneously resolve.[lvii] However, it is important to note that even with treatment AGW can be recurrent. Smoking cessation is paramount to help reduce the burden of AGW. One of the goals of vaccine programs is to develop “herd immunity” so that AGW never occur in the first place.[lviii]

There are several options for treatment depending on number and size of lesions and mode of application (self-applied or clinician-applied); each have their own respective application requirements, effectiveness, cost, and side effects. Tables 1 and 2 in the following link provide current options on treatment: https://www.canada.ca/en/public-health/services/infectious-

[4] One study found the quadrivalent vaccine to be 100% effective in protecting against anogenital warts in HPV naive females between 16 and 24 years; and another study found the quadrivalent vaccine to be 90% effective in HPV naive males between the ages of 16 and 24 (Human papillomavirus vaccination - UpToDate)

diseases/sexual-health-sexually-transmitted-infections/canadian-guidelines/anogenital-warts/treatment-follow-up.html#a2.3

For pregnant persons with AGW or a history of AGW, it is possible that the disease may worsen or recur. During pregnancy, the treatment options may be limited and less effective. Rarely a significant AGW growth during pregnancy raises the alarm for obstruction of the birth canal and/or vertical transmission to the fetus, resulting in juvenile onset respiratory papillomatosis.[lix]

There are NO screening programs for head and neck, penile or anal cancers

To illustrate how important HPV vaccination can be, it may be relevant to discuss with patients that, unlike cervical cancer, there are no organized screening programs for precancerous oropharyngeal, anal, or penile cancers. Accepting the HPV vaccine can play an important role in disease prevention.[lx]

As it relates to oropharyngeal cancers, regular dental examinations play an important role in identifying and testing pre-cancerous or suspicious lesions. CAF Dentistry oral examinations include clinical oral cancer screening. When there is a suspected oral lesion, biopsies can be obtained by the dental provider. CFHS Dental professionals may recommend HPV vaccination in conjunction with regular dental health exams and additional preventative care.

In November 2023, there was a consensus guideline published by the International Anal Neoplasia Society (IANS) for anal cancer screening, specifically for higher-risk populations that are disproportionally affected by anal cancer.[lxi] The incidence of anal cancer in the general population remains low and not everyone should be screened. Within the guideline, the high-risk groups identified were: people living with HIV, men who have sex with men, transgender women, patients with a history of vulvar precancer or cancer, and patients with a history of solid organ transplant. This consensus guideline includes screening tools such as digital anal rectal examination, cytology, HPV test, and/or high-resolution anoscopy (if appropriate and available). The decision to screen these high-risk groups (and potentially others) should consider the available local resources. For more details on the IANS anal screening guidelines refer to: https://onlinelibrary.wiley.com/doi/epdf/10.1002/ijc.34850.

At present there are no routine screening tests or programs for penile cancers.

In addition to HPV vaccination, what are other prevention strategies?

In addition to HPV vaccination, the following are other prevention strategies to help reduce the risk of obtaining an HPV infection and/or improve the chance of clearing it.

Cervical cancer:

- **Encourage routine cervical cancer screening:** Regardless of HPV vaccination status, all persons with a cervix should receive routine cervical cancer screening (i.e. HPV test/Pap test). Those who have had a total hysterectomy due to high-grade dysplasia (HSIL and above) should also continue to have vaginal vault screening based on relevant guidelines.[lxii]
- **Reduce factors that increase the risk of cervical cancer**: Counselling and supporting patients with smoking cessation, including nicotine containing e-cigarettes, can reduce the risk of persistent HPV infection.[lxiii] Patients can be counselled to utilize barrier protection (i.e., condoms) to lower the risk of HPV transmission.

Oropharyngeal cancer

- **Encourage routine dental exams**: Routine dental exams support regular screening for oral cancers. Good oral hygiene also reduces the risk of chronic gingival inflammation, which can be entry points for viruses like HPV.[lxiv]
- **Reduce factors that can increase risk of oropharyngeal cancers**: Patients should be counselled and supported in their effort to stop smoking cigarettes including nicotine containing e-cigarettes as these can increase the risk of persistent HPV infection. Additionally, patients should be encouraged to limit alcohol consumption and inhaled cannabis use, and to utilize sexual practices that can reduce HPV transmission, such as the use of barrier protection (i.e., dental dams). [lxv] [lxvi] [lxvii]

Anal cancer

- **Encourage regular health visits**: For certain populations it will be important to maintain regular health visits to ensure any signs or symptoms of anal cancer are investigated in a timely way. HPV vaccination is strongly encouraged for these patients. Smoking cessation and other harm reduction strategies should be reviewed when appropriate.[lxviii]
- **Reduce the factors that increase the risk of anal cancer**: Patients can be counselled to utilize barrier protection (i.e., condoms) to lower the risk of HPV transmission.

Cervical cancer screening using HPV testing

Cervical cancer screening is transitioning towards HPV primary testing rather than the Pap test in Canadian provinces. At present there is no national strategy so each province will have their own modified algorithm. The CFHS is also looking at options for implementation. The testing will be similar to the Pap test using the same collection process, but there will be opportunity for a self-swab option. HPV testing is a more accurate test. It has a higher sensitivity and a higher negative predictive value (lower chance of a false negative) than the Pap test. This means that it is more accurate at identifying people at risk of developing pre-cancerous lesions. Also, it is more accurate at detecting cervical cell changes earlier and therefore, the interval for screening can be increased from every 3 to every 5 years with a negative test result in average-risk populations.[lxix]

> “HPV testing is a more accurate test. It has a higher sensitivity and a higher negative predictive value (lower chance of a false negative) than the Pap test.”

Therapeutic vaccines are being studied to help cure existing HPV infection

The current vaccines are for prevention only; however, research is underway for therapeutic HPV vaccines. [5]

[5] Currently the licensed prophylactic vaccines utilize viral-like particles (VLP) for the L1 capsid protein of the papillomavirus, which prevent 90% of HPV infections. There are therapeutic HPV vaccines being developed and studied. Most of them focus on the E6/E7 tumor proteins. There are four categories of treatment vaccines: 1) live vector-based vaccines, 2) peptide and protein-based vaccines, 3) nucleic acid-based vaccines and 4) whole cell vaccines. These have been effective in pre-clinical studies, but not yet in clinical studies (Yan et al., 2023; Mo et al. 2022).

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