TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP, INNOVATION AND ACTION IN PUBLIC HEALTH.

—Public Health Agency of Canada

Également disponible en français sous le titre :
RÉCOMMENDATIONS RELATIVES AU PROGRAMME DE VACCINATION CONTRE LE VIRUS DU PAPILLOME HUMAIN

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BACKGROUND
The Canadian Immunization Committee (CIC) was established in 2004 to provide a national forum for public health to implement the objectives of the National Immunization Strategy, improve the effectiveness and efficiency of immunization programs, address emerging immunization issues, and foster federal/provincial/territorial (F/P/T) cooperation, collaboration and engagement of non-governmental stakeholders. It reports to the Communicable and Infectious Disease Steering Committee (CIDSC) of the Pan-Canadian Public Health Network (PHN).

STATEMENT OF PURPOSE
This document is intended to support provincial and territorial decision-making with respect to the implementation or expansion of human papillomavirus (HPV) immunization programs.

METHODOLOGY
In response to expanded indications for the quadrivalent HPV vaccine, as well as with the introduction of a new bivalent HPV vaccine, a multidisciplinary CIC HPV Task Group was established in July 2010 to develop an updated and comprehensive document on recommendations for HPV immunization programs. The CIC HPV Task Group was made up of a chairperson (Dr. Paul Van Buynder) as well as representatives from the CIC and experts in HPV, vaccinology, public health, sexual health, cancer and sexually transmitted and infectious disease control. The Task Group was supported by a secretariat at the Public Health Agency of Canada. The document is built upon items from the analytical framework for immunization programs in Canada by Erickson, De Wals and Farand (1). In 2012, the CIC commissioned a systematic review of the literature to Brisson and Drolet to examine the cost-effectiveness of HPV immunization program expansion (2). Their review provided much needed and extensive evidence to formulate the cost-effectiveness section of this document. A draft of this document was developed by CIC HPV Task Group members. In June 2013, information contained in the February 2013 draft of the CIC Recommendations for HPV Immunization Programs was presented at the HPV Consensus Meeting and served as the foundation for discussion among HPV experts, policy makers and decision makers in attendance at the meeting. The current document represents the cumulative work described above along with the input of the participants at the June 2013 meeting. This document was approved by the CIC in December 2013, the CIDSC in February 2014 and the PHN in March 2014.

DISEASE CHARACTERISTICS AND BURDEN OF ILLNESS
The characteristics of HPV infection and burden of disease are described in detail in the National Advisory Committee on Immunization (NACI) 2007 statement (excerpts reprinted below with permission) on HPV vaccine and in the subsequent 2012 update (3, 4). A summary of information is provided below; please refer to the NACI documents for the complete review.

NATURE AND CHARACTERISTICS OF THE INFECTIVE AGENT
There are over 100 different types of HPV, each consisting of circular DNA molecules wrapped in a shell made up of two protein molecules. Human papillomaviruses infect differentiating epithelial cells of skin or mucosae, with at least 40 HPV types able to infect the anogenital tract. Almost all cervical cancers can be traced to infection with oncogenic HPV types, including types 16 and 18. These types are referred to as high risk (HR) because of their link to cancer, including cervical cancer. In addition to the HR types, there
are other HPV types, in particular 6 and 11, that are referred to as low risk (LR) types for causing cancer, but that cause the majority of genital warts (3).

CLINICAL MANIFESTATIONS AND COMPLICATIONS

Human papillomaviruses are capable of causing benign and cancerous anogenital disease as well as benign and malignant head and neck lesions. HPV infections are transmitted sexually by direct epithelial (skin or mucosa) to epithelial contact and vertically to an infant exposed to the virus in the maternal genital tract; as well, transmission from oral mucosal contact in head and neck infections is likely (3).

Cervical dysplasia and cancer are the potential consequences of genital infection with HR oncogenic HPV subtypes. The rapidly replicating nature of the cervical transformation zone appears to make this area more susceptible to oncogenic influences. HPV infects the cervical cells, and types 16 and 18 contribute to 70% of the incidence of cervical cancer (5). Cervical cancer appears to develop in a progressive fashion; usually mild dysplastic changes evolve into severe dysplastic changes and ultimately into in situ carcinoma and, if untreated, invasive squamous cell carcinoma (SCC) (3). The time it takes for an infection to progress to invasive cervical cancer can vary widely, with typical progression estimated to take up to 10 years or longer (6). In rare cases, however, lesions appear to progress rapidly with invasive cancer developing in < 1 year (7).

It is of note that most immunologically competent women who are infected with oncogenic HPV will clear the infection without its progression to cervical carcinoma. There is evidence that approximately 40% of undiagnosed cervical intraepithelial neoplasia, grade 2 (CIN 2) will regress over 2 years, but CIN 2 caused by HPV type 16 may be less likely to regress than CIN 2 caused by other high risk HPV genotypes (8).

HPV types 16 and 18 have also been implicated in the much more rare cancers of the penis, anus (9), vulva and vagina, in which mechanisms of oncogenicity are presumed to be similar to those of the cervix. HPV types 16 and 18 are also associated with cancers of the mouth and oropharynx. Although squamous cell cancers of the mouth and oropharynx are rare, 35.6% (range 11% to 100%) of oropharyngeal, 23.5% (range 4% to 80%) of oral and 24% (range 0% to 100%) of laryngeal cancers have been associated with HPV (10).

HPV infection can also result in anogenital warts (AGW), primarily due to types 6 and 11. Genital warts are flat, papular, or pedunculated growths that can occur anywhere on the genital skin surface but typically on the vulva, penis and perianal skin. They are usually self-limited lesions in immunocompetent individuals, resolving in 12 to 24 months. It is estimated that HPV types 6 and 11 cause 70-90% of genital warts (11) and 20-50% of cases involve co-infection with oncogenic HPV types (11-13). The virus enters the epithelium, usually through a break, and then infects and replicates in basal and parabasal cells. Progeny virus are created, which shed at the epithelial surface.

Recurrent respiratory papillomatosis (RRP) is also linked to HPV. It is a rare condition, characterized by recurrent warts or papillomas in the upper respiratory tract, particularly the larynx. Almost all cases of RRP are linked to HPV types 6 and 11 (14, 15). For additional information on RRP, please refer to the NACI 2007 statement on human papillomavirus vaccine (3).

EPIDEMIOLOGY OF THE DISEASE

HPV is often described as the most common sexually transmitted infection (STI) (16). It is not a notifiable disease in Canada. 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/human immunodeficiency virus (HIV) clinics and university health clinics.
The total burden of HPV-associated cancers among both genders is estimated at 5.2% of all cancers worldwide (17). An assessment by the International Agency for Research on Cancer (IARC) concludes that, in addition to convincing evidence that multiple HPV types, including types 16 and 18, cause nearly all cervical cancers, data show a causal role of HPV type 16 in cancers of the vulva, vagina, penis, anus, oral cavity, and oropharynx, and some association with cancers of the larynx and periungual skin, as well as an association of HPV type 18 with cancer at most of these sites. Types 6 and 11 are not implicated in the development of cervical cancer, but are associated with SCC of the larynx and with uncommon Buschke-Löwenstein tumours of the penis and anus (18).

EPIDEMIOLOGY IN FEMALES

HPV prevalence and incidence
The 2012 NACI update on HPV describes recent Canadian prevalence data. Moore and colleagues estimated HPV type prevalence among females, using the largest Canadian population-based sample to date (BC women aged 13-86 years, n=4821) (19). Overall HPV prevalence was 16.8% (95% CI: 15.8-17.9). The prevalence of vaccine types 6, 11, 16 and 18 was 4.0 % (95% CI: 3.5-4.6), 0.2% (95% CI: 0.1-0.4) 10.7% (95% CI: 9.8-11.6) and 3.5% (95% CI: 3.1-4.1), respectively. Overall HPV positivity (both high and low-risk types) was most prevalent in women under 20 years of age with a significant trend of decreasing prevalence (any HPV type, any high-risk, and any low-risk type) seen until 60 years of age (p<0.0001 for each) (19). These overall prevalence estimates are comparable to other studies.

A seroprevalence study in BC with women aged 15 to 39 years undergoing prenatal testing detected HPV type 16 and 18 antibodies in 17.9% and 9.5% of subjects respectively; 3.9% of the sample group had antibodies to both types (20). The authors concluded that exposure to HPV types 16 and 18 occurred relatively soon after becoming sexually active. The neutralizing antibody titres were maintained across all age groups, possibly due to persistent infection, re-infection, or long-term antibody persistence.

For additional information on prevalence and incidence of HPV in females, including international data, please refer to the two NACI statements on HPV vaccines (3, 4).

There are very few studies of HPV incidence in Canada among women. The 2007 NACI statement describes results from two incidence studies conducted in Ontario (21) and in Quebec (22). In the Ontario study of women aged 15 to 49 years (mean 32.7 years) with a mean interval of 14 months of follow-up (range 9 to 21.3 months), incident HR HPV infection was found in 11.1% of women who were initially HPV negative. The highest incidence was found among those aged 15 to 19 years (25.0%), followed by those 30 to 34 years (14.7%) (21). In the Quebec study, female university students (mean age of 23 years; range 17 to 42 years) were followed at 6-month intervals for 24 months. The cumulative rate for new HPV infections was 36% during the 2-year period of the study, taking into account co-infection with more than one HPV type; 29.0% were infected with HR types and 23.7% with LR types. The most frequently detected incident HPV types were 16 (5.2 cases/1,000 woman-months), followed by 84, 51, 53 and 54 (22).

HPV prevalence estimates for women in countries around the world range from 2% to 44%, depending on the geographic region, population sampled and testing methodology. A peak prevalence of HPV infection in women less than 25 years of age has been consistently demonstrated, with a decreasing prevalence with age thereafter. Herrerro et al. found that among this group oncogenic HPV types predominated, whereas in women greater than 55 years old, non-oncogenic and uncharacterized types were the most common (23).

For additional information on prevalence and incidence of HPV in females, including international data, please refer to the two NACI statements on HPV vaccines (3, 4).
Epidemiology of cervical cancer

Globally, cervical cancer is estimated to be the second most common malignancy affecting women. In 2005, approximately 1 million women were estimated to have cervical cancer, and more than 250,000 deaths were attributed to the condition worldwide (24). Older women in developing countries suffer disproportionately from cervical cancer, with the global 2005 estimated incidence rate among women aged ≥ 70 years at 70 per 100,000 and the estimated mortality rate 60 per 100,000.

In Canada, the incidence of cervical cancer varies with age. Incidence initially peaks among women in their 40s, then declines and peaks again among women ≥ 70 years of age. Canadian incidence and mortality rates associated with cervical cancer have declined since the 1970s, attributable to the success of cytology screening efforts begun in the 1960s (3).

Approximately 70% of cervical cancers arise from the squamous cells, and 18% to 20% arise from the glandular cells (adenocarcinomas). Adenosquamous carcinomas account for approximately 5% of cervical cancers and share features of both SCC and adenocarcinoma. Other unspecified types of cervical cancer account for the remaining 5% (5).

Despite the overall decline in the incidence of cervical cancers, a study of provinces with complete and consistent registries of histological classification (Ontario, Saskatchewan and British Columbia) has shown that incidence rates of adenocarcinoma and adenosquamous carcinoma increased, from 1.30 and 0.15 per 100,000 women respectively in 1970-1972 to 1.83 and 0.41 per 100,000 women respectively in 1994-1996 (25). These increases were mainly observed in women aged 20 to 49 years. The incidence rates of cervical adenocarcinoma among older women decreased slightly.

Although still relatively rare, the increasing incidence of adenocarcinoma is of concern because of the poorer prognosis compared with that for SCC (26-28). A positive test for high-risk HPV is a highly significant risk factor for both adenocarcinoma and SCC (29). These carcinomas also represent an additional challenge for screening, as clinical and epidemiologic studies suggest that cytology screening is less effective in detecting adenocarcinoma than SCC because the former arise further in the endocervical canal.

Infections with multiple HPV types

There is relatively little data on the prevalence, incidence or natural history of multiple HPV infections; important information when considering multivalent vaccines. Epidemiologic studies have noted that infection with a given type does not decrease the probability of being infected by phylogenetically related types (16). While studies have shown that 20% to 30% of women with cervical HPV infections have multiple types present, regardless of cytology/pathology, cervical cancer is typically a monoclonal event related to one HPV type (30).

EPIDEMIOLOGY IN MALES

HPV prevalence and incidence

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 (3). Despite limitations in determining HPV status in males, infection and asymptomatic HPV cases appear to be common. HPV DNA testing from genital sites measures only current infections which are typically transient, and can vary widely due in part to variation in the type and number of anatomic sites sampled (e.g. single vs. multiple sites), use of different analytical methods, and the selection criteria of the populations studied (31).

There are few published Canadian studies of HPV prevalence or incidence among men. One study by Ogilvie et al. reported a prevalence of any HPV type from any site (glans penis/foreskin, penile shaft, scrotum) of 69.8% in a STI clinic population of heterosexual males in Vancouver, BC (32). Weaver et al. compared subsets of males and females (18 to 20 years of age) attending the same university in the
United States and found a prevalence of 28% for both sexes (33). A review of 12 studies by Partridge and Koutsky reported prevalence of HPV among males ranging from 3.5% to 45.0% (34). The prevalence of HR types ranged from 2.3% to 34.8%, with type 16 the most prevalent in all but one study (34). The prevalence of LR infections ranged from 2.3% to 23.9%, and prevalence of multiple infections ranged from 3.4% to 22.6%. In the HPV in Men (HIM) study, HPV type 16 was the most common oncogenic type detected (6.5%), followed by HPV type 51 (5.3%) and HPV type 59 (5.3%) (31).

**Epidemiology of HPV-associated cancers**

Among cancers affecting men, it is estimated that HPV infection is associated with 80-90% of anal cancers, 40-50% of penile, 35% of oropharyngeal and 25% of oral cavity cancers (17, 35, 36). Among HPV-associated cancers, approximately 92% of anal cancers, 63% of penile cancers and 89% of oral cavity and oropharyngeal cancers are attributable to high-risk HPV types 16 and 18 (17). In particular, individuals with AGW have a higher risk for anal cancer than the general population (37, 38).

For more information on the epidemiology of HPV-associated cancers in males, please refer to the 2012 NACI update on human papillomavirus vaccines (4).

**HPV and men who have sex with men (MSM)**

HPV infection and associated anal disease is highly prevalent among MSM, particularly in those who are HIV-positive. In the San Francisco Men’s Health Study (SFMHS), anal HPV DNA was detected in 93% of HIV-positive (regardless of CD4 count) and 61% of HIV-negative MSM (39). HIV-positive participants were at significantly increased risk of HPV DNA positivity (relative risk (RR)= 1.5; 95% CI: 1.4-1.7) compared with those that were HIV-negative. Prevalence of high-risk HPV types 16 and 18 was 38% and 28% for HIV-positive participants and 19% and 3% for HIV-negative participants respectively. Infection with high-risk HPV types is associated with anal intraepithelial neoplasia (AIN) and may be related to persistence of infection due to interaction between HIV and HPV (40-43).

Overall increases in anal cancer among MSM observed over the past few decades may be related to longer life expectancies in HIV positive men on highly active antiretroviral therapy (HAART). Rates of anal cancer among HIV-positive MSM are approximately 70 per 100 000 person years, which exceeds cervical cancer rates among women even in areas of the world with the highest rates of cervical cancer (44).

**Impact of male HPV infection on female infection and disease**

Sexual intercourse with HPV infected males is associated with increased risk of precancerous lesions and cervical cancer in women (45-51). In a case control study of women with cervical cancer and their male partners conducted by Bosch et al., a five-fold increase in odds of cervical cancer was observed among women whose partners tested positive for the presence of HPV DNA (adjusted OR=4.9; 95% CI: 1.9-12.6) (46). Risk of cervical cancer was also significantly associated with lack of circumcision in male partners, which is known to significantly increase the risk of HPV infection (48).

A recent Canadian study evaluating the influence of a partner’s HPV infection status and sexual practices on prevalent infection among new couples found that current partner’s status was the most important risk factor for prevalent infection (52). Burchell et al. assessed participants of the HITCH (HPV Infection and Transmission among Couples through Heterosexual activity) study whose primary subjects were women attending university or college in Montreal and their partners. Overall, prevalence of HPV infection was 56%, with higher prevalence among those with infected partners (83%) compared to those whose partners were not infected (19%) (n=263 couples) (52). Another publication based upon the HITCH study reports high type-concordance between newly-formed partnerships (41%), nearly four times more than expected if HPV status of partners were not correlated (53).

There are limited studies that directly demonstrate reduced transmission of HPV vaccine-types from males to females, or reduced cervical cancer, as a result of immunization of males (54-56). Modeling studies have estimated the impact of HPV immunization of males with varying assumptions and results. A
transmission dynamic model by Elbasha et al. predicted that while a quadrivalent HPV vaccine program targeting females prior to 12 years of age would result in a reduction in the incidence of genital warts by 83% and of cervical cancer by 78%, the addition of males to this program would result in a small further reduction with a resulting total decrease of 97% for AGW and 91% for cervical cancer (57). Another transmission-based dynamic model (58) assessing cost-effectiveness of quadrivalent HPV vaccine in Mexico examined various HPV immunization strategies for 12 year old females. The most effective strategy was found to be immunization of 12 year olds, with a temporary catch-up program immunizing both sexes of ages 12-24 years (58).

Another model explored the optimal age at immunization and pattern of vaccine introduction in Finland (59). The authors found that, once the full impact of immunization is reached, the annual proportion of HPV type 16-associated cervical cancer cases prevented was expected to be 67% if immunization of girls occurred at age 15 years, and/or 68% if it occurred at age 12 years, assuming 70% coverage. If immunization occurred at age 12 years, immunizing males as well as females was estimated to prevent an additional 15% of cases annually, if male coverage is 30% (59).

Two additional models were based upon roll-out of bivalent HPV type 16/18 vaccine (not currently licensed in Canada for use in males). Taira et al. predicted that inclusion of males into an age 12-year old female program further reduces cervical cancer cases by 2.2%, above and beyond a 61.8% reduction in cervical cancer cases for females only (60). A cost-effectiveness analysis by Kim et al. estimated that including males in a bivalent HPV immunization program provided an additional 4% cancer reduction beyond a reduction of 63% predicted for females alone (61).

**EPIDEMIOLOGY OF ANOGENITAL WARTS (AGW)**

AGW represent a considerable public health issue with respect to quality of life and economic burden for both males and females. Two recent publications provide important baseline data in terms of the epidemiology of AGW in Canada. Kliewer et al. and Marra et al. both linked population-based hospital and physician databases to estimate the incidence and prevalence of AGW in Manitoba and BC respectively (62, 63).

Both studies reported a significant burden of AGW disease, with incidence rates of 154 per 100,000 in men and 120 per 100,000 in women (Manitoba, 2004) (62) and 131 per 100,000 in men and 121 per 100,000 in women (BC, 2006) (63). Prevalence estimates were also comparable at 146.4/100,000 (165.2/100,000 for men and 128.4/100,000 for women) in Manitoba on December 31, 2004 and 148/100,000 (157 per 100,000 in men and 140 per 100,000 in women) in BC on December 31, 2006. In both studies, prevalence and incidence of AGW were consistently higher among men compared to women with the peak of incidence occurring between 20 and 24 years of age for women and 25 to 29 years of age for men (62, 63).

A twenty year time trend analysis in Manitoba showed a peak in AGW incidence in 1992 followed by a decline, with rates increasing slightly in more recent years, particularly among men. The male:female incidence rate ratio increased over time from 0.76 in 1985 to 1.25 in 2004 (62).

In BC, the mean length of an episode of AGW was estimated at 69 days (2.5 months) with the average length of an episode significantly longer in men compared to women (76 days versus 61 days, p<0.001). The average cost of treatment per episode was $C190 translating to an estimated annual, direct medical cost in BC of approximately $C1 million (63).

**EPIDEMIOLOGY OF RECURRENT RESPIRATORY PAPILLOMATOSIS**

Recurrent respiratory papillomatosis (RRP) is a rare condition characterized by recurrent warts or papillomas in the upper respiratory tract. Almost all cases of RRP are linked to HPV types 6 and 11. RRP can result in substantive morbidity (3). A Canadian national database was developed by Campisi et al. to track cases of juvenile onset RRP (JoRRP) (64). The national incidence of JoRRP was 0.24 per 100,000
children aged 14 years and younger, with the natural history of JoRRP following a nonlinear time course with 64% of cases having a decreasing annual rate of surgery over time (64).

For more information on the epidemiology of RRP, please refer to the 2007 NACI statement on human papillomavirus vaccine (3).

**SPECIFIC POPULATIONS AFFECTED AND RISK FACTORS**

**RISK FACTORS FOR HPV IN FEMALES**

Within Canada, HPV prevalence varies with age, place of residence and ethnicity. In a Montreal study, the overall prevalence of HPV infection was found to be strongly associated with place of birth; women from western Canada, Ontario and Europe were more likely to be infected with any HPV than women born elsewhere (65).

Women from northern Canada have been reported to have higher rates of HR HPV infection and cervical cancer. Many of these women are also of aboriginal (Inuit) ethnicity, and HPV infection appeared to be acquired at an earlier age in Inuit versus non-Inuit individuals (21, 66, 67). Available studies indicate that Indigenous peoples are disproportionately affected by HPV infections, are at a greater risk for HPV-related genital cancers, are more likely to be diagnosed at a later stage in the disease process, and remain less likely to survive a diagnosis of cervical cancer than non-Indigenous peoples (68, 69). HPV type 18 is most prevalent in Aboriginal women, and is significantly more common in Aboriginal than non-Aboriginal women (70).

**RISK FACTORS FOR HPV 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 (3). HPV prevalence among males has been shown to vary by the sex of their sexual partners (71), the presence of cervical pathology in their female partners and geographic region (72). The most consistent factor associated with increased risk of acquisition of HPV infection among males is the lifetime number of sexual partners (73-75). A significant protective effect associated with circumcision is reliably reported in the literature (73-77). Nielson et al. reported that among participants of the HIM study, condom use during less than half of all sexual encounters was associated with increased risk of HPV compared with condom use during more than half of all sexual encounters (adjusted odds ratio [OR]= 2.03; 95% CI: 1.07-3.84) (78).

**CURRENT DISEASE TREATMENT AND PREVENTABILITY**

Most HPV infections are asymptomatic and self-limiting, clearing within 24 months. However, persistent infections with oncogenic types may lead to cancer. This process typically takes a number of years or even decades. Survival rates vary according to treatment and stage at the time of diagnosis (79).

*Cervical cancer:* There are many avenues for cervical cancer prevention in Canada. Immunization is considered to be part of a primary prevention strategy and cervical cancer screening part of a secondary prevention method (79). The ability of Papanicolaou (Pap) smear screening to detect cervical dysplastic changes prior to the development of carcinoma has led to dramatic reductions in invasive cancer in the developed world. Even with effective vaccine programs, until close to 100% immunization coverage can be achieved for all oncogenic HPV types this ability to detect pre-invasive disease will remain critically important (3).

Treatment for cervical cancers depends on the stage of the cancer. Surgical treatment ranges from tissue removal by cone biopsy through to complete hysterectomy. Other treatment may include radiation therapy and/or chemotherapy (80).
**Vulvar and vaginal cancer:** Risk factors for vulvar cancer include infection with HPV and increasing age. Treatments for vulvar cancer include laser therapy, surgery, radiation therapy and chemotherapy. Risk factors for vaginal cancer include infection with HPV, increasing age, and prenatal exposure to diethylstilbestrol (DES). Treatments for vaginal cancer include surgery, radiation therapy and chemotherapy (81, 82).

**Cancers affecting men:** In addition to HPV, anal cancer among males is associated with lifetime number of sexual partners, receptive anal intercourse, HIV infection and cigarette smoking. Treatment for anal cancer may include surgery to remove all or part of the tumour and the surrounding tissue, chemotherapy and radiation therapy (83).

Penile cancer is rare, representing less than 1% of all male cancers. Aside from HPV infection, risk factors associated with penile cancer include smoking, lack of circumcision, phimosis, chronic penile inflammation and immunosuppression (4). Treatment for penile cancer may include surgery to remove only the cancerous tissue, or all or part of the penis, chemotherapy and radiation therapy (84).

**Anogenital warts:** Prevention strategies for AGW include condom use to prevent acquiring the HPV infection, and immunization for HPV. Most cases of AGW in immunocompetent individuals will eventually resolve on their own. Medical treatments consist of topical cream, cutting, freezing or burning the warts to remove them (84).

**PERSONAL AND SOCIAL IMPACT OF THE DISEASE**

HPV disease can have a significant effect on quality of life, as infection and testing results in social stigma, stress and anxiety. HPV infection can also lead to multiple types of cancers and the health-related effects of both the illness and the treatments, including potentially death.

For women, an abnormal cervical cancer screening result carries a significant psychosocial impact. The need for a repeat examination or treatment creates anxiety and entails substantial inconvenience for women (79).

Oropharyngeal cancers are associated with a significant impact on individuals requiring treatment for these conditions. Surgical resection often results in alterations in speech and swallowing. Chemoradiation is the preferred method of treatment but is associated with a higher mortality. Survival rates for these cancers are generally low with a three year rate of 55% to 62% and a five year rate of 22% (85).

AGW represent a considerable public health issue with respect to quality of life and economic burden for both males and females. A study by Marra et al. (86) used standardized questionnaires to assess health-related quality of life (HRQoL) among 75 subjects in Vancouver, BC, with a history of AGW. Low HRQoL associated with AGW was substantial and comparable in magnitude to some well-delineated chronic diseases such as genital herpes (86). In Drolet et al (87), 272 patients with a first or recurrent episode of AGW were recruited from the clinical practices of 42 physicians across Canada. AGW had the greatest negative impact on usual activities, pain/discomfort, and anxiety/depression, and on self-image, sexual activity, and partner issues and possible transmission. The median duration of a first AGW episode amongst incident cases was 125 days and resulted in quality-adjusted life years (QALYs) lost of 0.017 to 0.041, which is equivalent to 6 to 15 days of healthy life lost.

**ECONOMIC IMPACT OF THE DISEASE**

The economic impact of HPV-associated diseases includes the direct costs of hospital care, drugs, physician services, expenditure in other institutions and administration, as well as indirect costs, including those associated with years of life lost, and short-term and long-term disability. The cost of disease screening must also be factored into an economic estimate (88).
The BC Cancer Agency estimated the annual direct costs associated with HPV type 6 and 11 related
diseases to be approximately $9 million, representing 18% of the total annual direct cost of HPV-related
diseases in BC (89). A Quebec survey found that AGW are associated with significant clinical burden,
with an average of 2000 patients treated each year, and 2.8 treatments required per episode (37).

VACCINE CHARACTERISTICS

Characteristics of the two vaccines that have been authorized for use in Canada are provided in detail in
the 2012 NACI statement. Readers are referred to that statement for a full description. Briefly, there are
two HPV vaccines authorized for use in Canada: Gardasil® and Cervarix™.

Gardasil® has been approved for females aged 9 to 45 years for the prevention of infection caused by
HPV types 6, 11, 16, and 18 and the following diseases or lesions associated with these HPV types (90):
- cervical, vulvar and vaginal cancer,
- genital warts,
- 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,
- cervical intraepithelial neoplasia (CIN) grade 1.

Gardasil® is indicated in females aged 9 to 26 years for the prevention of (90):
- anal cancer caused by HPV types 16 and 18,
- anal intraepithelial neoplasia (AIN) grades 1, 2, and 3 caused by HPV types 6, 11, 16 and 18.

Gardasil® is indicated for males aged 9 to 26 years for the prevention of infection caused by HPV types 6,
11, 16 and 18 and the following diseases associated with the HPV types included in the vaccine (90):
- anal cancer caused by HPV types 16 and 18,
- genital warts (condyloma acuminate) caused by HPV types 6 and 11,
- anal intraepithelial neoplasia (AIN) grades 1, 2, and 3 caused by HPV types 6, 11, 16 and 18.

Cervarix™ has been approved for females aged 9 to 25 years for the prevention of cervical cancer
(squamous cell cancer and adenocarcinoma) by protecting against the following precancerous or
dysplastic lesions caused by oncogenic HPV types 16 and 18 (91):
- cervical intraepithelial neoplasia (CIN) grade 2 and grade 3,
- cervical adenocarcinoma in situ (AIS),
- cervical intraepithelial neoplasia (CIN) grade 1.

NATURE AND CHARACTERISTICS OF THE HPV VACCINES

Gardasil® is a quadrivalent HPV vaccine (HPV4 vaccine) consisting of the L1 capsid protein of each of
four HPV strains (types 6, 11, 16 and 18). The vaccine is administered as a 0.5ml dose containing the L1
protein components of the four strains. The virus-like particles of each type are purified and adsorbed
onto an aluminum-containing adjuvant (90).

Cervarix™ is a bivalent HPV vaccine (HPV2 vaccine) consisting of L1 capsid proteins of two HPV
genotypes (types 16 and 18). The vaccine is administered as a 0.5ml dose containing the L1 protein
components of the two strains. HPV2 contains a novel proprietary adjuvant, AS04, which works on the
innate and adaptive immune pathways. In comparison to the aluminum adjuvant, AS04 induces a stronger
adaptive immune response with higher antibody levels and genotype specific memory B cells following
immunization (91). The clinical significance of this is unknown.
HPV4 and HPV2 vaccines cannot cause disease because they contain no live biologicals or DNA and are not infectious. They have been shown to be safe and generally well tolerated (92-95). In clinical trials, systemic adverse events such as headache or fatigue were reported by a similar proportion in the vaccine and placebo recipients (3).

IMMUNE RESPONSE

A brief summary of data from the 2012 NACI statement is included below. Please see the NACI statement for complete details (4).

Immunogenicity has been assessed in females aged 9-45 (96) and males aged 9-26 (97) immunized with HPV4 and for women aged 10-45 immunized with HPV2 (98-101). The seroconversion rate 1 month after the second dose exceeded 97.5% for all types of HPV included in the vaccine (98). Robust anti-HPV geometric mean titres (GMTs) were observed at this time. One month following the administration of a third dose of vaccine, nearly all participants (≥ 99%) had developed antibodies against the types of HPV contained in the vaccines. The antibody levels after immunization were found to be 10-100 times higher than the levels produced by natural infection. Correlates of protection are unknown, however comparative studies have shown that the average anti-HPV GMTs in preadolescents and adolescents aged 9-14 were twice those in women aged 15-25 (98). One month after the second dose of HPV4, GMTs against all virus types included in the vaccine in youths aged 10-15 were higher than the GMTs observed 1 month after the third dose in women aged 16-23 (98). The clinical significance of this is unknown. The vaccine was well tolerated in both age groups.

In a head-to-head immunogenicity study comparing HPV2 and HPV4 vaccines, women (age groups of 18-26, 27-35, 36-45 years) were randomized to receive either the HPV2 or HPV4 vaccine (102) and results reported most recently at month 24. In the according-to-protocol cohort for immunogenicity, seropositivity rates of neutralizing antibodies were, across all age strata, 100% (HPV2 vaccine) and 97.5–100% (HPV4 vaccine) for HPV type 16, and 99.0–100% (HPV2 vaccine) and 72.3–84.4% (HPV4 vaccine) for HPV type 18. Corresponding geometric mean titers (GMTs) were 2.4–5.8-fold higher for HPV type 16 and 7.7–9.4-fold higher for HPV type 18 with the HPV2 vaccine vs. the HPV4 vaccine; HPV type 16 and HPV type 18 GMTs were significantly higher with the HPV2 vaccine than the HPV4 vaccine (p < 0.0001) in the total immunized cohort (received ≥1 vaccine dose, irrespective of baseline sero/DNA-status). Similar results were obtained using enzyme-linked immunosorbent assay (ELISA). Positivity rates and GMTs of antigen-specific IgG antibodies in cervicovaginal secretions (ELISA) were not significantly different between vaccines. At month 24, CD4+ T-cell responses for HPV type 16 and HPV type 18 were higher with the HPV2 vaccine; memory B-cell response was higher for HPV type 18 with the HPV2 vaccine and similar between vaccines for HPV type 16. Both vaccines were generally well tolerated. Although an immunological correlate of protection has not been defined, differences in the magnitude of immune response between vaccines may represent determinants of duration of protection (102).

Efficacy data are not available for the 9-13 age group since most are not sexually active and it is considered unethical to perform pelvic examinations. However, immunogenicity results showing high antibody response in young girls would support non inferiority in protection as compared with older age groups.

Studies examined the extent of immune memory in response to a primary immunization series for both the quadrivalent and the bivalent HPV vaccine (103, 104). Both vaccines induced an anamnestic response when challenged. The authors concluded that HPV vaccine induced high efficacy and stable anti-HPV levels for at least five years. When administered on a schedule of three doses over six months, both vaccines elicited an immune response substantially greater than the immune response seen after natural HPV types 16 and 18 infection (105).
VACCINE EFFICACY AND SHORT-AND LONG-TERM EFFECTIVENESS

EFFICACY IN FEMALES

Clinical trials published to date have shown a decrease in the incidence of HPV type 16 and 18 infections, CIN 1 and CIN 2/3, vaginal and vulvar cancers, and genital warts following HPV immunization (99, 106, 107).

The longest follow-up after vaccination in clinical trials for females is 5.5 years for the quadrivalent vaccine (101, 108) and 9.4 years for the bivalent vaccine (109). In a quadrivalent vaccine study, the prophylactic administration of the HPV4 vaccine had high efficacy in preventing persistent infection with HPV types contained in the vaccine, AIS and CIN 2/3 related to the vaccine types, as well as against external genital lesions such as AGW, VIN and VaIN. A subset of participants in the study was followed for 60 months after dose 1 with high sustained vaccine efficacy and no evidence of waning immunity (101, 108). From the peak antibody titres 1 month after dose 3, there was a detectable decline in antibody levels until about month 18, when the titres appeared to plateau for the rest of the 5-year follow-up period. This plateau was well above the titres observed in women who had naturally acquired HPV infection for types 11 and 16 but was approximately the same as for natural infection for types 6 and 18 (108).

After administration of HPV2 vaccine, participant outcomes are available for phase II and phase III trials (110, 111). Phase II analysis reported HPV2 vaccine efficacy against six and 12 month-persistent HPV type 16/18-cervical infections of 96% and 100% (100). At a follow-up period of up to 7.3 years, vaccine efficacy against HPV types 16/18-CIN 2+ was 100%, resulting from zero cases in vaccinees and nine cases in controls (111). Final, event-driven analysis of a phase III trial at 3 years of follow-up indicated HPV2 vaccine efficacy against six and 12 month-persistent HPV types 16/18 infection of 93.8% and 91.2% (112). There were four cases of HPV type 16/18-CIN 2+ identified in vaccinees and 56 cases among controls.

For additional information on vaccine efficacy in females, please refer to the 2007 and 2012 NACI statements on human papillomavirus vaccine (3, 4), as well as the 2007 CIC statement on an HPV immunization program (79). As well, more information on vaccine efficacy in females is presented below, in a comparative analysis of the bivalent and quadrivalent vaccines, with a specific focus on cross-protection.

COMPARATIVE VACCINE EFFICACY OF THE BIVALED AND QUADRAVILENT VACCINES IN THE CONTEXT OF A FEMALE-ONLY PROGRAM IN CANADA† (113)

Large clinical trials have shown near 100% vaccine efficacy against precancerous lesions associated with the vaccine HPV types (99, 101, 106, 112). Though the virus-like particles in the vaccines were designed to generate HPV type-specific antibodies, the phylogenetic similarities between L1 genes of different types (e.g. HPV type 16 with HPV types 31, 33, 52, and 58, and HPV type 18 with HPV type 45) create the possibility of a cross-reactive immune response elicited by the vaccine (114). Recent trials have reported vaccine efficacy against non-vaccine HPV types, suggesting a cross-protective effect (100, 112, 113, 115, 116).

Cross-protection afforded by the HPV vaccines is among the key factors being examined in differentiating between the two vaccines for public programs (117, 118). It will likely play a role in the choice of vaccine for public immunization programs (113). However, differences in trial designs and in the characteristics of studied populations in terms of prevalence and distribution of HPV infection at baseline complicate the comparison of cross-protection between the bivalent and quadrivalent vaccines (113). Malagon et al. conducted a systematic review of the literature to summarize and compare the clinical trial evidence.

† Analysis for the comparative efficacy of the HPV vaccines has been provided by a systematic review conducted by Malagon et al, 2012.
existing for the cross-protective efficacy of the bivalent and quadrivalent vaccines among HPV naive populations (113). HPV type-specific vaccine efficacy among HPV naive populations (DNA negative for all tested HPV types) was chosen for comparisons as it best represents the true prophylactic effect of immunization (i.e., vaccine efficacy is minimally diluted by the presence of females who are infected or immune at baseline, which may vary between trials) (113).

In the Malagon systematic review, the primary outcome of interest was to evaluate and compare the vaccine efficacy of the bivalent and quadrivalent vaccines against ≥6-month persistent infections and CIN 2+ associated with non-vaccine HPV types (HPV types 31, 33, 45, and 58) (113). A total of five clinical trials were evaluated, including two for the HPV4 vaccine and three for the HPV2 vaccine. For CIN 2+ outcomes, they extracted efficacy estimates both including and excluding lesions that were co-infected with HPV types 16/18. Co-infections with more than one HPV type are frequent (119), and in these cases it is difficult to determine the specific type causing the lesion. This may lead to bias due to misclassification of the lesion's causal HPV type (120, 121). Type-specific vaccine efficacy measures reported in clinical trials generally include all lesions detected with the HPV type of interest, including those with co-infections. HPV type 16 has the highest prevalence of infection in cervical lesions (122, 123), and HPV type 16 and HPV type 18 have greater risks of progression than other types (124, 125), which suggests that most lesions co-infected with HPV types 16/18 are attributable to these types (113). As co-infections with HPV types 16/18 will be rare in the vaccine arm but frequent in the control arm, this can potentially lead to overestimates of efficacy against non-vaccine types (120, 121). Given this, they provided a more conservative estimate of effect, calculations of vaccine cross-protective efficacy excluding lesions co-infected with HPV types 16/18 were presented (126). The secondary outcomes of interest were efficacy against ≥6-month persistent infections associated with HPV types 16/18, and against CIN 2+ associated with all non-vaccine types combined (113).

Malagon qualitatively examined the heterogeneity of the different trials by comparing the trial designs, settings, population characteristics and durations of follow-up. Since the main objective of the systematic review was to compare the vaccine efficacies against non-vaccine HPV types between the bivalent and quadrivalent vaccines, they decided, a priori, not to pool the efficacies of the two vaccines. However, they quantified the heterogeneity between the most comparable trials to examine whether any differences observed in vaccine efficacy between the two vaccines could be attributed to chance alone. They also examined the heterogeneity between the different trials of the same vaccine (113).

The most comparable populations were the quadrivalent FUTURE I/II trial restricted modified intention to treat population 2 (RMITT2) (106, 127) and the bivalent PATRICIA trial total immunized cohort of naive population (TVC-naive) (112, 126). Both were sub-populations of subjects in large international efficacy trials followed on average for 3.6 years, restricted post-randomization to females HPV-naive to 14 HPV types at baseline, cytologically normal at baseline, serologically negative to the corresponding vaccine types, and who had received at least one vaccine dose (113).

Type-specific vaccine efficacy against 6-month persistent infections

The PATRICIA bivalent trial produced higher point estimates of efficacy against 6-month persistent HPV types 31, 33, and 45 infections than the FUTURE I/II quadrivalent trial (113). Significant quadrivalent vaccine efficacy was observed against HPV type 31 persistent infections (46.2%, 95% CI 15.3-66.4) in the FUTURE I/II trial (113). For the bivalent vaccine, significant efficacy was observed against HPV type 31 (77.1%, 95% CI 67.2-84.4), HPV type 33 (43.1%, 95% CI 19.3-60.2), HPV type 45 (79.0%, 95% CI 61.3-89.4), and HPV type 52 (18.9%, 95% CI 3.2-32.2) in the PATRICIA trial (106, 112, 126, 127).

Type-specific vaccine efficacy against CIN 2+

The PATRICIA bivalent trial showed higher point estimates of efficacy against CIN 2+ associated with HPV types 31, 33, and 45 than the FUTURE I/II quadrivalent trial (113). Though all trials evaluated efficacy against CIN 2+, only FUTURE I/II and PATRICIA evaluated efficacy against CIN 2+ excluding
lesions co-infected with HPV types 16/18. Significant quadrivalent vaccine efficacy against CIN 2+ associated with HPV type 31 was observed when lesions co-infected with HPV types 16/18 were included (70.0%, 95% CI 32.1-88.2). This efficacy was lower and non-significant when lesions co-infected with HPV types 16/18 were excluded (57.4%, 95% CI -2.0-83.9) (113). In PATRICIA, significant efficacy against CIN 2+ associated with HPV types 31, 33, and 45 (from 82.3% to 100.0%) was observed when lesions co-infected with HPV types 16/18 were included (113). When these co-infected lesions were excluded, only efficacy against CIN 2+ associated with HPV type 31 (83.4%, 95% CI 43.3-96.9) and HPV type 33 (76.3, 95% CI 35.5-93.0) remained significant (106, 112, 126, 127).

Both the quadrivalent and bivalent HPV vaccines showed significant cross-protection in HPV-naive populations (113). The quadrivalent vaccine showed consistent efficacy against outcomes associated with HPV type 31, while the bivalent vaccine showed consistent efficacy against outcomes associated with HPV types 31, 33, and 45. For both vaccines, there was very little evidence of substantial cross-protection against other HPV types. Differences in estimates were observed between the vaccines, with the bivalent vaccine presenting higher efficacy against HPV types 31, 33, and 45 across both outcomes, though the differences were not always statistically significant. Finally, significantly lower efficacy against 6-month persistent infections with HPV type 31 and 45 was observed for longer bivalent trials, which may imply waning of cross-protection (113).

The results of this systematic review are supported by plausible biological rationales. First, the phylogenetic similarities between L1 genes from vaccine and non-vaccine types (HPV type 16 with HPV types 31, 33, 52, and 58 (A9 species), and HPV type 18 with HPV type 45 (A7 species)) (128) create the possibility of a cross-reactive immune response elicited by the vaccine types (114). Secondly, observed differences in cross-protection between vaccines may be due to different adjuvant systems. While the quadrivalent vaccine contains an aluminium hydroxyphosphate sulphate system, the bivalent vaccine contains an AS04 adjuvant system, which has been shown to enhance humoral and memory B cellular immunity compared to an aluminium salt alone (129). Thirdly, antibody titers remain generally high over time for HPV types 16/18 (102, 130) (except for HPV type 18 for the quadrivalent, which diminishes after 4 years) (101, 131) whilst the levels for HPV types 31, 33, and 45 reach much lower titers following immunization (102, 132, 133) and decline after 2 years either to the levels seen with natural infection or below the limit of detection (102). Although there is currently no immunogenicity threshold for vaccine protection, these observations suggest a potential for waning of cross-protection (113).

The higher estimates of efficacy of the bivalent vaccine against outcomes associated with HPV types 31, 33, and 45, may be due to true differences in cross-protection against these types, or may be due to differences between trials (113). The Malagon systematic review compared type-specific vaccine efficacies among HPV-naive women with similar eligibility criteria and durations of follow-up to minimize bias due to possible differences in type distributions, baseline prevalences of infection, and demographic factors between the vaccine trials (FUTURE I/II and PATRICIA). At baseline, both trial populations were similar in terms of age and lifetime number of partners, and were cytologically normal, seronegative against HPV types 16/18 and DNA negative against 14 HPV types. In addition, counting of events began after the first vaccine or control dose, and mean follow up was 3.6 years in both trials. However, differences between FUTURE I/II and PATRICIA trials remain. For example, incidence rates of infections were higher in the control arm in FUTURE I/II than those in PATRICIA, but type-specific incidence of CIN 2+ was almost identical. Differences in infection rates may be due to the fact that, in FUTURE I/II, both cervical and vulvar/perianal samples were tested for infection outcomes while in PATRICIA only cervical samples were tested, or may be due to differences in HPV DNA test sensibilities (113). It is unclear to what extent these differences can influence the magnitude of the differences in cross-protection between the HPV vaccines (113).

Estimates of vaccine efficacy against persistent infection with HPV types 31, 33, and 45 appear to decline in studies with longer follow-ups, although caution should be taken when interpreting these results as evidence of waning cross-protection (113). Substantial debate surrounds which outcome should be used
to measure true HPV vaccine efficacy (113). The value of infection outcomes has been extensively discussed (121). They:

1. are associated with the development of cervical lesions and cancer (134);
2. are more frequent and thus give more precise estimates of efficacy, and most importantly;
3. are not subject to misclassification bias due to co-infections with other HPV types (121).

However, efficacy against persistent infection may be diluted by undetected baseline infections or by trace contamination by an infected regular partner, and thus may not represent expected efficacy against disease (113). Clinicopathological outcomes such as high-grade precancerous lesions (CIN 2+) are closer surrogates for cancer, and are considered by some as a more medically meaningful endpoint. Unfortunately, lesion endpoints are vulnerable to various biases. Firstly, as stated earlier, presence of co-infected lesions can lead to misclassification bias. The inclusion of co-infected lesions with HPV types 16/18 can inflate the estimates of vaccine efficacy against lesions with non-vaccine types, as these co-infected lesions will occur frequently in the control arm but very rarely in the vaccine arm (113).

For the HPV types showing high and significant cross-protection against CIN 2+ when lesions co-infected with HPV types 16/18 are included, excluding these lesions produces only a moderate decline (113). Conversely, for the HPV types showing non-significant or low cross-protection against CIN 2+ when lesions co-infected with HPV types 16/18 are included, excluding these lesions produces an important decline in type-specific vaccine efficacy. These observations suggest that, though part of the observed efficacy against cross-protective types may be due to HPV types 16/18, a cross-protective effect still remains for some non-vaccine HPV types (113). Efficacy against all non-vaccine types combined also substantially declines when lesions co-infected with HPV types 16/18 are excluded. This may be explained by the fact that HPV types with significant cross-protection only represent a fraction of all non-vaccine types in CIN 2+ lesions, and efficacy against lesions with other non-vaccine types will mostly be due to efficacy against the HPV types 16/18 co-infecting the lesion (113). Efficacy against CIN 2+ is also subject to bias due to the competing risks of other HPV types. In a co-infected unimmunized individual, if an HPV type 16/18 infection progresses to CIN 2+ before a non-vaccine type progresses, the removal of the HPV type 16/18 lesion prevents the potential progression to CIN of the co-infecting non-vaccine type. Conversely, HPV types 16/18 associated lesions will be very rare among immunized individuals, leaving the possibility for the other non-vaccine types to progress to precancerous lesions. Hence, CIN 2+ rates associated with non-vaccine HPV types in the control arm will be underestimated compared to the vaccine arm, resulting in lower estimates of vaccine efficacy. However, this is not expected to substantially bias vaccine efficacy in trials, as these generally last only a few years and the risk of a non-vaccine type infection progressing to CIN 2+ within this time frame is very low (124, 125). Both infection and lesion outcomes would also be affected by the potential unmasking of types in the vaccine arm due to the removal of HPV types 16/18. This unmasking would lead to an underestimation of vaccine efficacy due to under-detection of non-vaccine types in the control arm. The potential magnitude of this bias is unknown and would depend on the sensitivity of the HPV DNA tests used in the trials (113).

Although over 25 modeling studies have consistently showed HPV immunization among pre-adolescent girls in developed countries to be cost-effective (135-137), very few have directly compared the bivalent and quadrivalent vaccines (118, 136, 138-141).

An original Canadian modelling study conducted in 2012 by Van De Velde et al., called HPV-ADVISE, examined the potential impact of differences in cross-protective efficacy between the HPV vaccines on population-level effectiveness at preventing HPV-related diseases. The model predicted that, under base case assumptions, immunizing 12-year-old girls (70% coverage) with the HPV2/HPV4 vaccine is predicted to reduce the cumulative incidence of AGW by 0.0% and 72.1%, respectively; diagnosed CIN 2 and 3 lesions by 51.0% and 46.1%, respectively; and cervical SCC by 31.9% and 30.5%, respectively, over 70 years (142).

In conclusion, results suggest that, though there remain some differences in design and in populations between trials, the observed higher cross-protection of the bivalent over the quadrivalent vaccine is most
readily explained by true differences in cross-protective efficacy between vaccines. While bivalent efficacy trials display lower estimates of cross-protection against infection over time, suggesting potential waning there is no reason that a similar impact would not be seen with HPV4. More research is required to examine the duration of cross-protective efficacy, and the potential impact of differences in cross-protective efficacy between the HPV vaccines on population-level effectiveness at preventing HPV-related diseases.

Efficacy in Males
Studies have shown HPV immunization has the potential to significantly reduce HPV-associated anogenital infection and disease in males (143, 144). A 2011 randomized, double-blind, placebo controlled trial by Giuliano et al. assessed efficacy, immunogenicity and safety of the quadrivalent vaccine against HPV infection and external lesions in males. The study included 4065 young men 16 to 26 years of age from 18 countries, of which 602 self-declared as having sex with men (MSM). Participants were randomized to receive the quadrivalent HPV vaccine or placebo at enrolment, month 2 and month 6 and were followed for a total of 36 months. The study results demonstrated that prophylactic administration of HPV4 was effective against incident and persistent HPV infection with types 6/11/16/18 (vaccine efficacy of 85.6%; 95% CI: 73.4%-92.9%) as well as reducing the incidence of HPV-related external genital lesions associated with HPV vaccine types (vaccine efficacy of 90.4%; 95% CI: 69.2%-98.1) in the study population (143). Although it is likely that the prevention of HPV infection will help prevent anogenital cancer, intraepithelial neoplasia, recurrent respiratory papillomatosis, and cancer of the oropharynx and HPV transmission, these outcomes were not directly demonstrated (143).

Palefsky et al. studied the safety and efficacy of the quadrivalent HPV vaccine against anal intraepithelial neoplasia associated with HPV types 6, 11, 16, or 18 infection in MSM. Their results showed that the vaccine was effective at preventing precancerous anal lesions associated with HPV vaccine types, including grades 2 or 3, in MSM (vaccine efficacy of 77.5%; 95% CI: 39.6%-93.3%) (144).

Efficacy in males 9 to 15 years of age was inferred by a pre-licensure immunobridging study published by Block et al. as well as analysis conducted by Merck (98, 145).

Efficacy in the Immunocompromised
There is very little data on the immunogenicity and efficacy of HPV vaccines in individuals receiving immunosuppressants. As with other vaccines, it is possible a satisfactory response is not obtained in these individuals (90, 91). Generally, vaccines are less immunogenic in immunocompromised individuals. However, seroconversion rates that were sufficiently high (≥95%) were observed in at least one study with the quadrivalent vaccine in individuals with HIV infection (146). In another study with the same vaccine, individuals with an inherited immune deficiency syndrome were observed with neutralizing antibody titres 64-80 times lower than immunocompetent individuals. Several other studies in immunocompromised individuals (147) are underway or have just been finalized and more robust data for these population groups are expected in the near future.

Coadministration with Other Vaccines and Medications
HPV4 and HPV2 vaccines are not live vaccines and have no components that have been found to adversely affect the safety or efficacy of other vaccines. Immunogenicity data shows an interaction between HPV and hepatitis B vaccines, resulting in lowered anti-HBs GMTs when compared with administration of the HB vaccine by itself. Overall, however, both co-administered and individual vaccines were generally well-tolerated and did not interfere with the immune response of either vaccine (148-150). Therefore, HPV vaccines can be administered at the same visit as other age-appropriate vaccines, such as the adolescent/adult formulation of Tdap, hepatitis B and meningococcal conjugate vaccines. More local reactions were observed when HPV4 has been administered with Tdap and Men4. Each vaccine should be administered using separate syringes at different anatomic sites (4).
In clinical studies on HPV vaccines, between 4% and 30% of participants were taking analgesics, anti-inflammatory drugs, antibiotics, antihistamines or vitamin preparations. The immunogenicity, efficacy and safety of the vaccine did not appear to be affected by these drugs (90, 91). In addition, 50 to 60% of participants were taking hormonal contraceptives. There is no evidence that use of hormonal contraceptives has an impact on the immune response (90, 91).

A small proportion (<1.8%) of participants in clinical trials have received inhaled corticosteroids, topically or parenterally. These drugs do not appear to influence the immune response to HPV vaccine (90).

SAFETY

The safety of both vaccines, including contraindication and precautions, has been thoroughly reviewed in the NACI statements and readers are referred there for a full description.

Agorastos et al. (151) reviewed available published and unpublished international post-marketing safety surveillance data reported for both quadrivalent and bivalent HPV vaccines. Based on this review, they concluded that both vaccines appear safe, with the majority of reported adverse events following immunization (AEFI) being local injection site reactions. No pattern of serious AEFI suggesting a causal relationship to immunization was observed.

EXISTING NACI RECOMMENDATIONS OR GUIDELINES FOR USE OF THE VACCINE AS OF JANUARY 2012

1. HPV vaccine (HPV2 or HPV4) is recommended for females between 9 and 13 years of age (NACI Recommendation Grade A). Vaccination between this age range covers most females prior to the onset of sexual activity. Immunogenicity bridging evidence implies that efficacy would be high.

2. HPV vaccine (HPV2 or HPV4) is recommended for females between 14 and 26 years of age (NACI Recommendation Grade A). Females in this age group are more likely to be sexually active, but would still benefit from vaccination as they may not have an HPV infection, and epidemiologic data indicates they are very unlikely to be infected with all HPV types contained in the HPV vaccine.

3. HPV vaccine (HPV2 or HPV4) is recommended for females between 14 and 26 years of age who have had previous Pap abnormalities, including cervical cancer and AGW (NACI Recommendation Grade B). While the vaccine does not have any therapeutic effect on pre-existing HPV infections or cervical disease, these women would still benefit from vaccination to HPV types not previously exposed to.

4. HPV vaccine (HPV2 or HPV4) may be administered to females over 26 years of age (NACI Recommendation Grade A (HPV4) / Grade B (HPV2)). Efficacy has been demonstrated for this group among those not infected with the relevant HPV types at the time of vaccination.

5. HPV vaccine is not recommended in females <9 years of age (NACI Recommendation Grade I).

6. HPV4 is recommended for males between 9 and 26 years of age for the prevention of AIN grades 1, 2, and 3, anal cancer, and AGW (NACI Recommendation Grade A). While cost-effectiveness needs consideration for a program of vaccinating males, there is good evidence that HPV4 decreases the incidence of infection, AIN, anal cancer and external genital lesions in males. In considering the potential inclusion of males in existing female-only routine HPV immunization programs, provinces and territories may consider the following:
• The public health and economic burden of AGW in Canada is considerable, particularly among men whose incidence rates and incidence rate ratios compared to females have been increasing in recent years (62, 63).

• The impact of vaccinating males, compared to that of improving vaccination uptake in existing female cohorts or vaccinating additional female cohorts.

• Inclusion of males in routine programs facilitates vaccination of males at a young age when the potential benefit of the vaccine is greatest.

• At this time, there are no studies that directly demonstrate that HPV vaccination of males will result in less sexual transmission of vaccine-related HPV types from males to females and in reduced incidence of cervical cancer. However, post-marketing preliminary findings from an analysis of vaccination status among the Canadian HPV Infection and Transmission among Couples through Heterosexual activity (HITCH) study participants suggest that female vaccination prevents transmission to men. In this analysis, a 2.7 fold protective effect against infection among male partners was shown, although confirmation using a larger sample will be required.

• While current models predict that addition of males to a routine HPV vaccination program would prevent additional cases of genital warts and cervical cancer among females to varying degrees, this is based on assumptions that such transmission from males to females will be reduced, rather than observational data.

• In addition, cost effectiveness needs consideration. Provinces and territories will need to compare the impact of vaccinating males with that of vaccinating additional female cohorts.

• While not directly comparable, lessons learned from gender-targeting of other vaccines should be considered. For example, like rubella, control of HPV among women may only be achievable through a gender-based (female only) vaccination policy if vaccine coverage among women is extremely high. Factors such as vaccine refusal, cost and weaknesses in vaccine delivery systems may support a gender-neutral (universal) policy to adequately control disease.

7. HPV4 is recommended in males between 9 and 26 years of age (NACI Recommendation Grade B) for the prevention of penile, perianal and perineal intraepithelial neoplasias and associated cancers.

8. HPV4 is recommended in MSM ≥9 years of age (NACI Recommendation Grade A). Early receipt of vaccine would confer maximum benefit, particularly since MSM may become infected with HPV more rapidly due to the high rate of infection in the population. However, MSM may still benefit from vaccination even when already sexually active, as they may not yet have HPV infection or exposure to all four HPV types.

9. HPV2 is not recommended in males at this time (NACI Recommendation Grade I). A recommendation for use of this vaccine in males will be made once data on efficacy endpoints are available.

10. There is insufficient evidence at this time to recommend a two-dose schedule of either HPV vaccine for females 9 to 13 years of age (NACI Recommendation Grade I).

11. While either HPV vaccine can be administered to persons who are immunosuppressed, the immunogenicity and efficacy of these vaccines has not been fully determined in this population and thus individuals may not derive benefit from these vaccines (NACI Recommendation Grade I). Further study is required.
12. HPV2 and HPV4 are not recommended for use in pregnancy (NACI Recommendation Grade I). Until further information is available, initiation of vaccine series should be delayed until after completion of a pregnancy. If a vaccine dose has been administered during pregnancy, there is no indication for any intervention.

13. HPV2 and HPV4 can be administered simultaneously with other adolescent vaccines (NACI Recommendation Grade A).

FEASIBILITY AND ACCEPTABILITY OF HPV IMMUNIZATION PROGRAMS

In a Canadian study to determine parental intention to immunize their daughters with the HPV vaccine, parents of children aged 8 to 18 were recruited from across Canada between June 2006 and March 2007 through random digit dialing (152). Participants were asked to respond to a series of questions in the context of a grade 6 (age 11-12 years), publicly funded, school-based HPV immunization program, including their intention to have their daughter immunized with the HPV vaccine. Of the 1,350 respondents, over 70% (73.8%, 95% confidence interval [CI]: 71.9%-75.7%) reported that they intended their daughter to be immunized against HPV. Across the country, in crude analysis, intention to immunize in different regions of residence ranged from 62.8% (95% CI 60.2%-65.4%) in British Columbia to a high of 82.6% (95% CI 80.6%-84.6%) in Atlantic Canada (p < 0.01) (152).

The most important predictor of parental intention to immunize was the psychological construct assessing parental attitudes towards vaccines in general and the HPV vaccine in particular. This construct examined aspects such as HPV vaccine safety and efficacy along with overall attitudes towards vaccines. Recommendations to immunize from health professionals, family and friends, and community leaders, with physicians in particular, were also important predictors (152).

Another study involved a self-administered questionnaire mailed to all obstetricians/ gynecologists and pediatricians, and to a random sample of family physicians in British Columbia, Quebec and Nova Scotia (1,268 respondents, response rate of 50.2%) (153). Most respondents intended to recommend the HPV vaccine; 95% felt that the vaccine should be given before the onset of sexual activity, and 80% felt that the best age for immunization was <14 years. Overall, 88% of Canadian physicians surveyed intended to recommend the vaccine if it was publicly funded and 84% if patients had to pay for it (153).

ACCESSIBILITY OF TARGET POPULATION/LEVELS OF UPTAKE

HPV vaccines are designed to prevent infection with HPV genotypes included in the vaccines but are not designed to treat women who have already been infected. Therefore, HPV immunization is best administered before the onset of sexual activity (3). School-based immunization programs remain an effective way to reach young girls and to make sure that all vaccine doses are administered (79). Published data suggest that immunization coverage with existing programs is high when school-based programs are used and higher in primary school than high school (154).

All provinces and territories in Canada have implemented publicly-funded HPV immunization programs (Table 1). However, reported HPV vaccine uptake varies across the country, ranging from around 60% in Alberta and Manitoba to approximately 85% in Newfoundland, Nova Scotia and Quebec (105).
### Table 1. Publicly funded HPV Immunization Programs in Canada (as of June 2013) (155, 156)

<table>
<thead>
<tr>
<th>Province</th>
<th>Year Implemented</th>
<th>Female cohort immunized</th>
<th>Catch-up</th>
<th>Immunization Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC</td>
<td>2008</td>
<td>Grade 6</td>
<td>Grade 9 (2008-2011)</td>
<td>2008/2009 – Grade 6 first dose: 64.7%; Grade 9 first dose: 66.4%*</td>
</tr>
</tbody>
</table>
| AB       | 2008             | Grade 5                 | Grade 9 (2009-2012) | 2010/2011 – Grade 5 three doses: 58%  
|          |                  |                         |          | 2011/2012 – Grade 5 three doses: 61.2% * |
| SK       | 2008             | Grade 6                 | Grade 7 (2008-2009) | 2008/2009 – Grade 6 (at least) first dose: 73% * |
| MB       | 2008             | Grade 6                 | ≤ Grade 10 (2012-2013) | 2011/2012 – Grade 6 three doses: 43.4 % * |
| ON       | 2007             | Grade 8                 | ≤ Grade 12 | 2008/2009 – Grade 8 three doses: 52.5%^  
|          |                  |                         |          | 2009/2010 – Grade 8 three doses: 55.2%^  
|          |                  |                         |          | 2010/2011 – Grade 8 three doses: 58.4%^  
|          |                  |                         |          | 2011/2012 – Grade 8 three doses: 70.2%^ |
| QC       | 2008             | Grade 4 (2 doses); third year of high school (1 dose) | Girls <18 years | 2011/2012 – Grade 4 two doses: 66-94% (mean 77%); Grade 9 three doses: 63-93% (mean 76%)* |
| NB       | 2008             | Grade 7                 | Grade 8 (2008-2009) | 2008/2009 – Grade 7 three doses: 71.9%  
|          |                  |                         |          | 2009/2010 - Grade 7 three doses: 71.2%  
|          |                  |                         |          | 2010/2011 – Grade 7 three doses: 73.7%  
|          |                  |                         |          | 2011/2012 – Grade 7 three doses: 75.8% * |
|----------|------|-------|-----------|---------------------|-----------|-----------|-----------|
| NS       | 2007 | Grade 7 | Grade 8 (2010-2011) | 2008/2009 – Grade 7 three doses: 77.1% | 2009/2010 - Grade 7 three doses: 59.8% | 2010/2011 – Grade 7 three doses: 74.8% | 2011/2012 – Grade 7 three doses: 76.1% |
| PE       | 2007 | Grade 6 | Grade 9 (2009-2010) | 2008/2009 – Grade 6 first dose: 80% (estimate) * | | | |
| NT       | 2009 | Grade 4 | Grades 9-12 or girls <22 years (2009-2014) | 2010/2011 – Grade 4 one dose: 54%; Grade 4 two doses: 52%; Grade 4 three doses: 47% * | | | |
| YT       | 2009 | Girls ≥9 years up to Grade 6 | Grades 7, 8 (2009-2011); free to girls ≥ 13 years to girls ≤ 18 years (starting in 2011) | 2011/2012 – Grade 6 one dose: 67% * | | | |
| NU       | 2010 | Grade 6 or girls ≥9 years | | | | | NA |

* as reported by provinces/territories to the Canadian Partnership Against Cancer (CPAC) as % receiving first dose in 2008-2009
* as reported by provinces/territories to the Canadian Immunization Registry Network (CIRN)
^ based on series coverage (i.e., 3 doses) as reported in provincial report (157)

If a booster dose is needed, it may be difficult to reach immunized women as there are no special immunization services for adults outside travel clinics and influenza immunization.
COST-EFFECTIVENESS OF HPV IMMUNIZATION PROGRAMS

In order to make informed decisions about immunization program implementation, it is important to consider the cost-effectiveness of immunization strategies. This is especially important when considering new programs or changes to existing programs (1). When the HPV immunization programs were first introduced in Canada, the vaccine was only approved for use in females aged 9-26 years. Since then, HPV4 has been licensed for use in males as well as in females up to the age of 45, and HPV2 has also been introduced. Cost-effectiveness analyses must thus consider the various options available. In this section, the cost-effectiveness of the two available vaccines is compared and discussed, as well as the cost-effectiveness of immunizing males.

COST-EFFECTIVENESS OF HPV IMMUNIZATION

COMPARATIVE COST-EFFECTIVENESS OF THE BIVALENT AND QUADRIVALENT VACCINES

While there is significant data available on the efficacy of the two HPV vaccines, what remains unclear is how much more jurisdictions should pay for the additional health benefit of HPV4, or conversely, how much lower the price of HPV2 needs to be for both vaccines to be equally cost-effective.

Two different approaches have been used in modelling studies. The net benefit approach (price difference for the genital warts component to be cost effective under a predetermined threshold) has been used a number of times in UK studies. An economic evaluation in the UK by Mark Jit and colleagues from the Health Protection Agency (HPA) (118), was an update to a previously published economic evaluation (158). The earlier (158) model of HPV transmission and disease was updated with recent evidence and expanded to include more scenarios with respect to vaccine characteristics such as duration of protection, cross protection, and end points prevented. For the base case analysis in the 2011 model, the vaccine price is set at £84.50 per dose, the mean list price for both vaccines. Immunization coverage was 80% in 12-13 year old schoolgirls for the full course of immunization (3 doses). Coverage for catch up cohorts was lower (65% for 13-17 year olds, 30% for 17-18 year olds). Both vaccines were cost-effective compared to screening only for most scenarios. HPV2 was not cost-effective at a price of £84.50 per dose when making pessimistic assumptions about duration of protection and end points prevented (118).

As tendered vaccine prices are unknown, preventing standard cost-effectiveness analysis comparing the two vaccines, the comparative analyses focus on the additional cost per dose of HPV4 at which both vaccines are equally cost effective. The 2011 UK analysis found that for both vaccines to be equally cost effective at a threshold of £30,000 per QALY gained, the additional cost of HPV4 ranges from £19 to £38 if both vaccines protect against all related cancer end points (118). If both vaccines protect only against licensed end points, the price differential is much greater (£48 to £68).

The 2008 economic evaluation from the UK using the same model (158) had reported a lower absolute price differential (£15 to £23, depending on duration of vaccine protection and whether or not there is a catch up program) than the 2011 study. Assuming lifelong protection and no catch up program, the absolute price differential at which both vaccines are equally cost-effective was £21 per dose. This would translate into a relative price reduction for HPV2 compared to HPV4 of 26% (at the 2008 UK list price of HPV4 of £80.50).

The alternative approach is to use an equal cost effectiveness approach. This assesses the price at which both vaccines are equally effective; in this scenario the price difference will decrease as prices go down. Using this methodology an Irish cost-utility analysis (140) reported that HPV2 needs to be 22% cheaper than HPV4 to be equally cost-effective. However the Irish study did not take herd immunity effects into
account, which may underestimate the relative price differential. Earlier studies assumed lifelong immunity and include cervical cancer and AGW outcomes.

Van de Velde et al. in their HPV-ADVISE modelling looked at demographic factors, sexual behaviour and HPV transmission, the natural history of genital warts and HPV-related cancers, immunization, screening, diagnosis and treatment and economic factors. They found that the use of the quadrivalent vaccine would lead to a reduction over a lifetime in the cumulative incidence of genital warts by 62% versus no impact from the bivalent vaccine. Smaller comparative cumulative reductions in CIN 2/3 and cervical cancer of 4-5% were seen if the bivalent vaccine was used compared to the quadrivalent. No differences on other cancers were observed between the HPV vaccines (142).

The quadrivalent vaccine’s protection against AGW appeared economically more important than possible advantages of the bivalent vaccine in cancer prevention. Brisson et al. concluded that if priced similarly, the HPV4 vaccine will be more cost-effective than the HPV2 vaccine, due to the quadrivalent vaccine’s protection against AGW (159). The magnitude of the price difference depends on the costs and QALY lost to AGW (159). In their earlier work, which did not take into account cross-protection, Brisson et al. found that if the HPV4 vaccine was $400 per three dose course the HPV2 would need to be about $295 for the two to be equally cost effective, a differential of 26% (139).

If we assume lifelong protection by both HPV vaccines, and no catch-up program, HPV2 may be equally cost effective as HPV4 under the following scenarios (160):

1. When the assumptions favour HPV2 (both vaccines protect against all related cancer end points and/or non-cancer outcomes for HPV4 are excluded) then the price of HPV2 is required to be 22% to 43% lower than HPV4 in order to be equally cost effective (160).

2. When assumptions do not favour HPV2 both vaccines protect only against licensed end points (cervical cancer for HPV2, cervical, vaginal, vulvar, and anal cancer as well as warts and mild smears for HPV4) then the price of HPV2 is required to be 54% to 77% lower than HPV4 in order to be equally cost effective (160).

It is biologically implausible to suggest that HPV2 would only protect against licensed end points and not against other HPV related cancers. Therefore comparisons should be based on comparative cancer protection versus additional HPV non-cancer protection with HPV4.

The recent original modeling study by Van de Velde et al. used more detailed Canadian input data for immunization coverage and disease (142). The authors found that, using an assumed Canadian population of 30 million individuals, a quadrivalent immunization program of 12-year-old girls with 70% coverage would prevent 1.9 million diagnosed AGW cases in men and women, 560,100 diagnosed CIN 2 and CIN 3 cases, and 20,800 SCC cases over 70 years. Switching to the bivalent vaccine would produce a rebound in diagnosed AGW cases (increase cases by 1.8 million) but would prevent an additional 42,600 diagnosed CIN 2 and CIN 3 cases and 1,400 SCC cases over the same period. Given the long time-lag between the age at immunization and disease, the full benefit in prevention of CIN 2 and CIN 3 and cervical cancer by switching to a bivalent vaccine was not expected for 20–40 years after the start of the immunization programs (142). These predictions assumed lifelong vaccine protection. If the duration of cross-protection was shorter for both vaccines, then the bivalent and quadrivalent vaccines were predicted to produce very similar vaccine effectiveness against HPV-related cancers. If the bivalent vaccine conferred substantially greater duration of protection than the quadrivalent vaccine, important incremental benefits would occur (142).

The relatively small incremental benefit of the bivalent vaccine over the quadrivalent vaccine, when duration of protection is similar, is explained by the fact that more than 70%–80% of cervical cancers and 90% of other HPV-related cancers are due to HPV type 16 and HPV type 18, against which both vaccines are highly efficacious (142).
In summary, the relative price difference between the two vaccines needed for equivalency with this goal varies with the assumptions made in the model inputs. The sensitivity analysis, including vaccine efficacy and duration, immunization coverage and timing, the disease burden and the disease endpoints considered suggests that on average this will yield a benefit for HPV4 usage of about $30 (161).

COST-EFFECTIVENESS OF THE INCLUSION OF MALES IN AN HPV IMMUNIZATION PROGRAM IN CANADA

All provinces and territories have implemented publicly-funded HPV immunization programs for girls, however some are considering program expansion to include males. Some jurisdictions have already moved forward with such expanded programs. The cost-effectiveness of such an expanded HPV immunization program needs to be examined.

In 2012, Brisson and Drolet performed a systematic review of the literature for the Canadian Immunization Committee, examining the incremental cost-effectiveness of adding boys to the existing girls-only HPV immunization program in Canada (2). In their review, it was noted that the burden of HPV related diseases in men is significant; the rate of HPV infection in males is similar to that of females (162, 163) and the lifetime risk of being infected exceeds 70% for males (164, 165). Infection with HR HPV in males has been associated with anal, penile and oropharyngeal cancers with, respectively, 83%, 49% and 47% of these cancers being HPV positive in North America (85, 166). The sex-specific incidence of these cancers remains relatively low in Canada (incidence rates of 1.4, 0.9 and 5.2 per 100,000 years for the incidence of anal, penile and oropharyngeal cancers, respectively (167)); however, this translates to an estimated 660 newly diagnosed HPV related cancers among men each year in Canada (191 anal, 68 penile and 401 oropharyngeal cancers) (168). In addition, using Manitoba and British Columbia billing data, there are an estimated 33,000 medical consultations for AGW by men each year in Canada (62, 63). A disproportionately high burden of HPV-related diseases has been described for MSM (2). Recent data suggest that the risk of persistent HPV infection and of developing external genital lesions are about 3-fold higher for MSM than heterosexual males (143, 169) and the risk of anal cancer is 17 times higher in MSM compared to heterosexual males (41).

The quadrivalent vaccine is authorized for use in males aged 9 to 26 years in Canada (90). The key criteria when making decisions about adding males to public health programs include the preventable burden of the disease, and the efficacy, safety, effectiveness and cost-effectiveness of the intervention (1). The systematic review by Brisson and Drolet (2) summarizes the evidence on the cost-effectiveness of immunizing boys against HPV in developed countries, the details of which are stated below.

Cost-effectiveness of immunizing boys against HPV† (2)

The systematic review by Brisson and Drolet found a total of 8 publications that met the eligibility criteria of a/reporting incremental cost-effectiveness of immunizing boys against HPV in addition to girls; b/including cost per QALY-gained as an outcome; and c/being conducted in developed countries (2). Table 3 summarizes the evidence, which suggests that if immunization coverage is high in girls, including boys in an immunization program will not be cost-effective (2). Seven of the eight studies reported that the incremental cost per QALY-gained of immunizing boys was higher than accepted cost-effectiveness thresholds when immunization coverage was assumed to be higher than 50% among girls (60, 141, 158, 168, 170, 171). When immunization coverage was assumed to be lower than 50% among girls on the other hand, studies predicted that immunizing boys was cost-effective (60, 170). However, when immunization coverage is low to moderate in girls, increasing coverage in girls/women is predicted to be more cost-effective than including boys in an immunization program (57, 170). Results remained qualitatively similar even though cost-effectiveness ratios decreased when including all preventable HPV-related disease in the analysis (Table 3) (2).

† Analysis for the cost-effectiveness of immunizing boys against HPV has been provided by a systematic review conducted by Brisson and Drolet, 2012.
Table 2. Incremental cost-effectiveness ratio of immunizing boys against HPV in addition to girl-only immunization (Cost per QALY gained)³(2)

<table>
<thead>
<tr>
<th></th>
<th>Canada</th>
<th>US</th>
<th>U.K.</th>
<th>Denmark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost/course</td>
<td>$CAN 285</td>
<td>$US 300</td>
<td>$US 500</td>
<td>$US 400</td>
</tr>
<tr>
<td>Coverage¶</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-49%</td>
<td>x</td>
<td>42,000</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>50-69%</td>
<td>x</td>
<td>&gt;100,000</td>
<td>62,000</td>
<td>&gt;200,000</td>
</tr>
<tr>
<td>≥70%</td>
<td>434,000</td>
<td>&gt;150,000</td>
<td>115,000</td>
<td>290,000</td>
</tr>
</tbody>
</table>

³. All studies are dynamic transmission models assuming high vaccine efficacy (>90% against HPV infection and disease in girls & boys). Boys are assumed to be immunized at 12 years of age except for Elbasha (172) (males are immunized between 9 and 26 years of age) and Laprise (171) (boys are immunized at 9 years of age).

†. All=all HPV-related diseases were included in the analysis (genital warts, cervical lesions, cervical cancer and cancers of the anus, vagina, vulva, penis, head and neck)

¶. Immunization coverage

⁰. Assumes that 75% and 45% of girls and boys are immunized by 18 years of age, respectively. In an earlier study (57), using the same model, Elbasha et al. estimated that immunizing boys in addition to females (12-year-old girls with a catch-up to 24 years of age) would produce an incremental cost-effectiveness ratio of $US 41,000 per QALY-gained assuming a cost per course of $US 360, high vaccine efficacy, and 70% coverage, and including only cervical cancer and genital warts outcomes.
No published studies have examined the cost-effectiveness of immunizing boys against HPV in a Canadian context. However, a 2012 cost-effectiveness analysis conducted for the Québec Ministry of Health and Social Services (171) estimated that the incremental cost-effectiveness ratio of immunizing boys in addition to girls is $434,000 per QALY-gained, under the current girls-only immunization program in Québec (assumptions of the model included immunization coverage=80%, age at immunization=9 years of age, catch-up=14 years of age, and cost per dose=$95). The economic evaluation included most HPV-related health outcomes except recurrent respiratory papillomatosis (RRP) (i.e., genital warts, cervical lesions, and cervical, anal, vulvar, vaginal, penile and oropharyngeal cancers). The analysis also included the incremental benefit of immunizing boys on HPV-related diseases among MSM. In the best case scenario for male immunization (e.g., 10% of the male population assumed to be MSM and a high relative risk of HPV-related diseases in MSM versus heterosexual men), it was estimated that the incremental cost-effectiveness ratio of immunizing boys is $180,000 per QALY-gained (assuming $95 per dose and 80% immunization coverage). Under these best case assumptions, the cost per vaccine dose would have to be $29 in order for the immunization of boys to be below the $50,000 per QALY-gained cost-effectiveness threshold (2, 171). The results of the systematic review by Brisson and Drolet strongly suggest that in Canada, where immunization coverage in girls is greater than 50% (173), immunizing boys in addition to girls is unlikely to be cost-effective under current HPV vaccine prices (2). The review also notes that in jurisdictions with lower immunization coverage (50-59%), increasing vaccine uptake among girls is likely to produce greater population-level effectiveness at preventing HPV-related diseases in females and males and to be more cost-effective than including boys in an immunization program (2). Finally, results of the review suggest that the price of the quadrivalent HPV vaccine would have to be substantially reduced to produce an incremental cost-effectiveness ratio below acceptable thresholds in Canada (i.e. $40,000-50,000 per QALY-gained) (2).

Herd immunity is the primary reason why most cost-effectiveness studies have predicted that immunizing boys is not cost-effective when coverage is moderate to high (above 50%) in girls (2). If coverage in girls is high, many of the boys who would receive the vaccine would never have become infected due to the herd effect of immunizing girls (55, 56). Therefore, including boys in an immunization program would produce considerable losses in immunization program efficiency, produce redundancy in vaccine delivery and increase cost-effectiveness ratios (2). Current evidence from Australia suggests that significant herd immunity effects are occurring in heterosexual males following girls-only HPV immunization programs (174, 175). If HPV immunization coverage among girls is low, the incremental gains by immunizing boys can be substantial; however, modelling studies show that increased immunization coverage among girls results in greater population-level effectiveness than adding boys to the immunization program (55, 56).

The systematic review by Brisson and Drolet found that there are two key elements that can reduce the predicted herd immunity impact of immunizing girls and thus increase the incremental benefit of immunizing boys and improve the cost-effectiveness of such a strategy (2). First, if immunized women can continue to be carriers and have transient infections, thus transmitting HPV, then herd effects may be smaller than predicted (2). Secondly, if coverage is low among subgroups of females that are highly sexually active, then herd immunity may be limited even though population level coverage is high (2). However, of note is that all models in the review assumed that immunization coverage and sexual mixing are independent, which may overestimate the incremental cost-effectiveness of immunizing boys (2). As vaccine uptake is likely to be associated with socio-demographic characteristics and sexual pairing is likely to be assortative, immunizing males will most likely lead to a high proportion of partnerships that have both members of the pair immunized (and a lower proportion of partnerships with at least one individual protected), thus reducing the incremental benefit of male immunization (55).

As mentioned earlier, the cost-effectiveness of immunizing boys is also sensitive to the cost of the HPV vaccine (2). Chesson et al. and Laprise et al. suggest that the price of the vaccine would have to be substantially lower than current prices to be cost-effective when immunization coverage among girls is high (>75%) (170, 171). In fact, under best case assumptions for male immunization, Laprise et al. estimate that the price of the vaccine would have to be lower than $29 per dose in order for the immunization of boys to be cost-effective in Québec (171).
Heterosexual males may benefit almost to the same extent as females from a girls-only immunization program due to herd immunity (55, 56). However, it is highly unlikely that immunizing girls will have an impact on HPV-related diseases among the MSM population. Therefore, girls-only immunization is likely to increase existing inequalities in the burden of HPV-related diseases among MSM and heterosexuals (2). More research is required to better identify the most effective and cost-effective strategies to reduce HPV-related diseases among MSM (2). Part of the challenge in conducting an efficient and cost-effective immunization program among MSM is that best results are gained when individuals are immunized at a young age and have not yet had exposure to HPV. However, most MSM have not identified as homosexual at the immunization age of about 12 years old (2).

Australia and the U.S. have recommended including males in their HPV immunization programs. In Australia, where the coverage is higher than 70%, reduction in vaccine prices are thought to have played a determining role in their recommendation (2). On the other hand, the Centers for Disease Control and Prevention (CDC) report that the immunization coverage of at least one dose in the U.S. is 44% and for three doses is 27% (30% among females interviewed at least 24 weeks after they initiated their vaccine series) (176). At this low immunization coverage of girls, immunizing boys is expected to be cost-effective, which partly explains the recent recommendation to immunize young men in the U.S. Another factor that may have played a role in the recommendation is the finding that HPV immunization of MSM would likely be a cost effective intervention for the prevention of genital warts and anal cancer (177). However, there are concerns with the modeling in this paper, and more research is required.

In summary, Brisson and Drolet conclude that modeling studies consistently show that immunizing boys against HPV is not cost-effective when immunization coverage is moderate to high among girls (above 50%) (2). These results are robust even when including the full burden of HPV-related diseases among males and the benefit of preventing disease among MSM in economic analyses. Hence, although immunizing boys can help further reduce the overall burden of HPV-related disease in females and males, at current prices immunizing boys may not be the best investment of scarce health care resources in Canada due to diminishing returns caused by herd effects (2). Future research should include examining the herd immunity effects from current girls-only HPV immunization programs.

Further consideration of MSM

Jurisdictions may wish to consider immunizing MSM and boys self-identified as homosexual, especially if immunization takes place prior to exposure to HPV. There is an equity issue with respect to immunizing males, as MSM would not receive the indirect protection from immunizing women only (178). Girls-only immunization is likely to increase existing inequalities in the burden of HPV-related diseases among MSM and heterosexuals (2). Target programs for high-risk men, including the MSM population, could represent a potential additional target for routine HPV immunization, but more research is required before making such a policy change (137).

A paper by Kim modelled the effect of HPV4 immunization in MSM at different ages (177). She suggested that in a scenario of HPV immunization of MSM at 12 years of age without previous exposure to HPV, compared with no immunization, immunization cost US$15,290 per QALY gained. In scenarios where MSM are immunized at 20 years or 26 years of age, after exposure to HPV infections, the cost-effectiveness ratios worsened, but were less than $50,000 per QALY under most scenarios. HPV immunization of MSM at 26 years cost $37,830 per QALY when previous exposure to all vaccine-targeted HPV types was assumed to be 50%. Outcomes were most sensitive to variations in anal cancer incidence, duration of vaccine protection, and HIV prevalence in MSM.

However, Kim models age and percentage exposed among those who will be exposed in their lifetime. Among heterosexuals, peak HPV incidence and sexual activity is 20-25 years of age and it is expected that over 50% of those who will be exposed in their lifetime will have been exposed before 20-26 years of age (for the average MSM the number is likely much higher). The Kim model predicts that immunizing MSM is not cost-effective when previous exposure is greater than 50% (177).
In practical terms, with an MSM program there would be a differential in who would receive the vaccine between the lower risk (those not exposed with lower sexual activity) or higher risk MSM (those with previous infection and with higher number of lifetime partners). If it is more the latter who are immunized, then immunizing MSM will be inefficient, ineffective and will not be cost-effective.

Immunizing MSM may be cost-effective given the high burden of HPV disease among these men, but much research is still required to accurately estimate the effectiveness and cost-effectiveness of such a strategy.

**COST-EFFECTIVENESS OF HPV IMMUNIZATION – A SUMMARY**

When comparing vaccine efficacy of the bivalent and quadrivalent vaccines in females, the evidence suggests that either vaccine can be used, despite considerations of the increased cross-protection afforded by the HPV2 vaccine and the protection against AGW afforded by the HPV4 vaccine. However, when factoring in cost-effectiveness, the quadrivalent vaccine is preferred unless the bivalent vaccine is priced at about $30 less per dose than the quadrivalent vaccine (161). This differential is independent of the cost of vaccine and is driven by the predicted additional benefits of protection against AGW (161).

Current cost-effectiveness data does not support the inclusion of all males in an HPV immunization program in Canada, where immunization coverage in girls is greater than 50%. However, if a male program targeted at high-risk boys and men (e.g. MSM) were initiated, HPV4 would be the vaccine product of choice, as it is the only one presently approved in Canada for use in males.

**ABILITY TO EVALUATE IMMUNIZATION PROGRAMS**

Erickson, De Wals and Farand emphasize the necessity to evaluate immunization programs in terms of their safety and population effectiveness (1). The evaluation of HPV immunization programs over time is thus extremely important, given the need to assess impact over the long term and, as with many other vaccine programs, the unknown duration of protection at the start of implementation. However, the ability to evaluate an immunization program must also be considered, because evaluation relies on a complex matrix of testing methodologies, reporting systems and registries. In light of this, monitoring and evaluating HPV immunization programs will require standardized HPV testing methods, standardized units of measurement for HPV antibodies, population-based reporting systems for HPV-associated diseases, and registries or information systems for follow-up of immunization coverage (179, 180). Effective linkage between the latter databases will also be important. Regular studies of the knowledge, attitudes and practices of the public and health professionals will also be necessary.

HPV immunization program evaluations in Canada include evaluations for BC, Ontario and Quebec. The BC evaluation (181) surveyed parents of girls enrolled in grade 6 during the academic year of September 2008-June 2009. Of the households who participated, 65.1% of parents reported that their daughters received the first dose of the HPV vaccine. In the same school-based vaccine program, 88.4% consented to the hepatitis B vaccine, and 86.5% consented to the meningococcal vaccine. This survey found that even with the removal of financial and health care barriers, parents are still hesitant to have their daughters receive the HPV vaccine (181). An evaluation of the Ontario school-based program found that many Ontario health units reported challenges in receiving support from local school boards. Despite this, vaccine clinics have been offered in all but two Ontario public school boards since 2007 (182). These findings indicate that strategies to ensure optimal HPV vaccine uptake need to be developed and employed (181).

Manitoba has implemented a comprehensive vaccine surveillance and evaluation system whereby females receiving the HPV vaccine through the school-based system are captured by the Manitoba
Immunization Monitoring System (MIMS). Those obtaining the vaccine outside the school system are captured by the Drug Program Information Network (DPIN) through the vaccine prescription (183). The immunization registry contains only non-identifying information such as the scrambled unique personal health identification number, date of birth, region of residence, date the prescription was filled, and date the vaccine was administered. Aside from being essential for an effective evaluation of the vaccine, the registry will also be an effective means of contacting immunized individuals if safety issues arise or if booster doses are required (183).

At a national level, much effort is still required to prepare for the evaluation of new HPV immunization programs, and little data is available in the literature. Infection with HPV is not reportable in Canada, so it is difficult to know the prevalence, incidence or distribution of HPV genotypes in the population (88). As for all immunization programs, provincial and national authorities will require a detailed evaluation plan for HPV immunization programs. Significant investments have to be made to conduct surveillance and program evaluation over the long term, and a multidisciplinary approach is needed.

AVAILABILITY OF SYSTEMS TO MEASURE COVERAGE AND VACCINE UTILIZATION, AND QUALITY OF IMMUNIZATION SERVICES

As with other health care programs, immunization is primarily a provincial and territorial responsibility. The Canadian Immunization Registry Network (CIRN), a federal/provincial/territorial working group of the CIC, have been working together for the past 9 years (since 2004) to develop a national network of immunization registries across the country. CIRN has developed the standards and guidelines for a common methodology to routinely measure coverage using registry data. Currently, approximately half of the provinces and territories have fully functional registries, and the remaining jurisdictions are either planning or evaluating options to implement an immunization registry. In the meantime, there are several alternatives for measuring coverage (79):

- The Adult and Childhood National Immunization Coverage Survey, conducted every 2 years, provides national estimates for 14 and 17-year-olds in the childhood survey and for the adult population. However, the concern with these studies is that they are not able to assess subpopulations and that non-participation bias cannot be excluded.

- Another alternative is to use provinces and territories with established immunization and cancer screening registries as special pilot sites. This approach would enable a more comprehensive assessment of immunization coverage, but data extrapolation to other provinces and territories may not be appropriate.

Immunizing adolescents or adults presents more barriers than immunizing young children. Because the HPV vaccine is recommended for adolescents and young adults, existing school-based immunization programs may require expansion, and the development of new immunization systems for young adults might be needed (79).

AVAILABILITY OF SYSTEMS TO MEASURE IMPACT OF HPV-RELATED INFECTIONS

Measuring the impact of the immunization program on HPV-associated diseases and on screening practices requires significant effort. A baseline assessment of HPV-associated diseases (including those caused by types not covered by the vaccine), of screening practices and of costs could be useful during the implementation of immunization programs (180) and the initial years. It is imperative to establish an HPV type distribution baseline that is representative of different populations across Canada and to follow this up with a long-term surveillance program to monitor the impact of HPV immunization against types 16 and 18 (and 6 and 11 if AGW are included) on the overall incidence and prevalence of HPV infections.
Ultimately, this surveillance system may reflect shifts in HPV type distribution as a result of immunization against types 16 and 18 (and 6 and 11 if AGW are included), such as an increase in types not included in the vaccine (79).

Planning for a national HPV sentinel surveillance system is under way. Surveillance includes repeated cross-sectional anonymous surveys of women (and/or men) recruited across Canada, linked to cervical/cervico-vaginal (and/or anal) specimens. This surveillance system will provide baseline data on the distribution of HPV subtypes in selected sites and populations across Canada in order to monitor the incidence and prevalence of type-specific HPV infections, to identify potential risk factors associated with high-risk HPV infection and to correlate the distribution of HPV types with cytological outcomes and socio-demographic and behavioural risk factors.

Although cervical cancer is the most important long-term health outcome, other endpoints are needed to monitor the short- and mid-term impact of immunization on HPV-related infections. Malignancies develop slowly, and although cancer registries are available they will be useful only years after the implementation of HPV immunization programs. Endpoints used in clinical studies could be used as short- and mid-term evaluation outcomes. A consensus report from a World Health Organization expert group proposed histologically confirmed high-grade CIN or worse (including cervical cancer) as an acceptable surrogate endpoint (179, 184, 185). Monitoring of cervical lesions will require development of population-based reporting systems for HPV-associated infections (180). Type-specific persistence of infection (the presence of the same HPV type at two or more consecutive visits separated by 6-12 months) could also be an outcome measure (179). However, commercial tests for HPV testing and typing are not yet routinely available in the Canadian public health system (79).

Evaluation plans should also monitor the HPV immunization impact on cervical cancer screening practices (decline in the burden of screen-detected precursor lesions requiring follow-up and treatment, new algorithms, etc.) and on continued screening compliance in HPV-immunized women.

In Canada, the national public health burden of condylomas is not known, and it is not a reportable disease. A provincial study from Manitoba examining trends over a 20-year period (62) reported 25,000 Manitobans diagnosed with AGWs between 1985 and 2004. The male:female incidence rate ratio increased from 0.76 in 1985 to 1.25 in 2004, with the highest incidence rate in those aged 20 to 24 years. Trends in prevalence were similar, with 2004 values of 165.2/100,000 for men and 128.4/100,000 for women. These population-based findings suggest that AGWs are a substantial burden to Manitobans and that their pattern has changed over time, with incidence and prevalence becoming higher in men than women (62).

AVAILABILITY OF SYSTEMS FOR LINKING HEALTH OUTCOMES DATABASES, IMMUNIZATION REGISTRIES AND POPULATION REGISTRIES

Evaluation of the HPV immunization program will be crucial and complex, requiring the development of a comprehensive plan and demanding significant resources (79). Even without national/provincial electronic immunization registries, it will be essential to be able to contact HPV-immunized women if an additional dose of the vaccine is needed. Relying on mass media and communication to professionals to disseminate information about the need for a booster dose would be less effective than individualized notification.

Canada Health Infoway supports the development of the Pan-Canadian Electronic Health Record, as well as the standardization of laboratory data (to ensure that data can be exchanged among systems), including cytopathology data. The immunization management module of the future PANORAMA public health information system could provide data on the HPV immunization status of residents in each
Canadian jurisdiction if the vaccine is provided by public health providers or if the immunization information is reported by private providers to public health authorities.

In the meantime, it may be possible to link existing regional/provincial databases (immunization and cancer) for evaluation. Also, national immunization coverage can be measured using the Adult and Childhood National Immunization Coverage Survey or by aggregating coverage estimates from the jurisdictions once the national coverage standards are adopted. The possibility of restricting certain aspects of the evaluation to predetermined geographic areas could be explored. Additional data from these areas could facilitate future decision-making on the prevention of HPV infections and related anomalies (79).

RESEARCH PRIORITIES

In their analytical framework, Erickson et al. state that new immunization programs are often implemented before important scientific questions can be resolved (1). When the national HPV immunization program was established between 2007 and 2010, it was recognized that research gaps existed, but that it was also important to avoid delays in offering HPV vaccines on a routine basis. However, it remains important that research gaps are addressed and answered in a diligent and timely manner.

RESEARCH PRIORITIES IDENTIFIED AT THE NATIONAL HPV RESEARCH PRIORITIES WORKSHOP

The National HPV Research Priorities Workshop that took place in Quebec City in November 2005 raised several knowledge gaps related to the HPV vaccine. The 10 highest-ranked research priorities were (4):

1. Most efficient way to deliver an HPV vaccination program
2. Knowledge, attitudes and beliefs, and acceptability of HPV vaccination programs in recipients, providers, parents
3. Vaccine program delivery costs
4. Immunogenicity of a two-dose HPV vaccine schedule
5. Impact of vaccination programs on cervical screening programs
6. How to promote HPV vaccine in an acceptable and effective way
7. Co-administration with other vaccines and effect of safety and immunogenicity
8. Economic burden of HPV-related diseases and conditions in Canada
9. Efficacy/effectiveness of a two-dose HPV vaccine schedule
10. As vaccine programs progress, observations with cervical screening programs

RESEARCH PRIORITIES IDENTIFIED BY NACI

Research priorities in addition to those identified in 2005 have been identified by NACI in their 2012 NACI statement. These include the following (4):

- Epidemiology and economic burden of male HPV-related diseases and conditions in Canada.
- Impact of HPV vaccination of males on sexual transmission of vaccine-related HPV types from males to females and on cervical cancer incidence.
• Mechanisms involved in the second peak in incidence among females later in life and subsequent risk of cervical cancer.

• Efficacy, effectiveness, and long-term immunogenicity of a two-dose HPV vaccine schedule for adolescents (females and males). The durability of immune response (antibody titres and immune memory) and efficacy of the two-dose schedule against infection and disease outcomes need to be determined.

• The clinical significance of the differences in the immune profiles of HPV2 and HPV4 is unknown. A head-to-head comparison of these two vaccine products, with a primary outcome of cancer protection, is warranted.

• Long-term impact of cross protection on disease outcomes following either vaccine.

• The efficacy of HPV vaccines in the prevention of head and neck cancers.

RESEARCH PRIORITIES IDENTIFIED BY EXPERTS IN JUNE 2013

At their meeting in June 2013, HPV immunization experts identified the following research topics, in addition to those previously presented by the 2005 Research Priorities Workshop and the 2012 NACI statement:

• Immunization coverage, focusing on those who are not being immunized and why.

• Cross-impacts of programming and immunization coverage for males and females, including exploration of whether the inclusion of male programs may help normalize HPV immunization, and with that, the impact on female immunization coverage rates.

• Effective means to improve uptake within hard-to-reach populations.

• Means to identify populations that might be at risk (e.g., women who are not being screened, and older or more isolated populations).

• Conceptual/analytical frameworks and criteria to assist in interpreting and understanding surveillance results.

• Identification, tracking and understanding of the knowledge, attitudes and beliefs of the public, including factors affecting the acceptability of HPV immunization within different population groups, age groups and circumstances, including socio-economic status.

In addition, the experts at the meeting noted that there should be a more collaborative and coordinated approach between provinces and territories in order to eliminate the real or perceived need to duplicate research efforts. It was agreed that this approach, along with establishing an effective means of sharing research finding, would facilitate more effective research and use of results.

INDICATORS FOR EVALUATING THE IMPACT OF HPV IMMUNIZATION ON THE POPULATION

Indicators are under development to support public health surveillance and program evaluation into the future. The indicators have been obtained through national consultations with the Screening Performance Indicators Working Group, the Cervical Cancer Prevention and Control Network (CCPCN), and have been supported by the Canadian Partnership Against Cancer (CPAC) and the Public Health Agency of Canada. These indicators are also platforms for ongoing research. The indicators under development cover the following objectives: 1) HPV vaccine uptake; 2) HPV prevalence (with and without disease); and 3) behaviour change in the vaccine era. The indicators currently focus on program evaluation and public health surveillance of the existing girls-only HPV immunization program; however, as jurisdictions consider and begin implementing other program strategies (involving males or new vaccines), these
indicators may require adaptation and expansion. As gaps in knowledge, best practices, and data collection methodologies are identified, research will be required.

OTHER CONSIDERATIONS

EQUITY AND ETHICAL CONSIDERATIONS

In Canada, social disparities exist in the utilization of cervical cancer screening (5), and cervical cancer affects mainly women of lower socio-economic status (186). A school-based immunization program could reduce these disparities by inclusion of all girls who go to school, without regard to their socio-economic characteristics. However, if no catch-up is implemented, such a program would remain inequitable for the teenagers outside the targeted school groups and for the women aged 15 to 45 years old who are not going to school but for whom HPV immunization is recommended (79).

Although males are not currently included in HPV immunization programs, they could be equally concerned about the possible effects of the virus on their health. Oncogenic HPV is strongly associated with cancers and high-grade dysplasias of the anogenital tract including the anus and penis, and is also associated with a proportion of oropharyngeal cancers. The sexual behaviour of males and their role in HPV transmission to women contributes to the disease burden in females. In addition, the herd immunity anticipated for heterosexual men from “female-only” immunization programs excludes protection in the MSM population (105). Globally, the incidence of HPV disease among MSM is increasing rapidly, with an estimated 95% of MSM who are HIV-positive also subject to anal HPV infection and consequently a significantly higher risk of anal cancer (105). Equity issues need to be considered in addition to cost effectiveness when deciding whether to include males in an HPV immunization program.

Because it is a sexually transmitted disease, HPV immunization could create an ethical dilemma regarding the concern about sending a morally wrong message, such as acceptance of sexual promiscuity. Immunization against hepatitis B, a virus that can also be transmitted through sexual contact, is now part of the publicly funded immunization programs offered in all provinces and territories (88). Even if similar concerns were raised, implementation of hepatitis B immunization programs has not prompted major parental opposition in Canada. In a review of relevant studies, only between 6% and 12% of parents were concerned about the impact of HPV immunization on the sexual activity of their child (187-190). Furthermore, safe sex and abstinence messages are not inconsistent with HPV immunization. Finally, HPV immunization is voluntary in Canada; its use should not be compulsory and not lead to school-based requirements (79).

IMMUNIZATION SCHEDULES

NACI recommends a three-dose schedule (0, 2 and 6 months) for the quadrivalent vaccine (3) and for the bivalent vaccine (0, 1 and 6 months). Currently, there is preliminary research available as well as research studies underway to assess other HPV immunization schedules (191, 192). As more information becomes available, provinces and territories may consider different schedules (e.g. extended schedules, two-dose schedules).

IMPACT OF IMMUNIZATION ON CERVICAL CANCER SCREENING

Cervical screening is an essential tool for evaluating the immunization program. While it is not within the CIC’s mandate to issue recommendations on cervical cancer screening, the introduction of immunization is expected to have a major impact ultimately on screening recommendations, and the two activities must now be planned simultaneously. An immunization program should constitute part of a comprehensive cervical cancer prevention program.
IMPACT OF HPV IMMUNIZATION ON SCREENING OUTCOMES

A lower prevalence of cervical lesions will result in a lower positive predictive value of cytology testing. HPV immunization could also have an impact on the use of new screening tests (e.g., tests to detect the viral DNA of various HPV genotypes). Finally, immunization is expected to reduce the colposcopy rate by reducing the risk of precancerous lesions (106, 127, 193). While HPV type replacement is a very low probability, CIC recommends the development of a surveillance system to detect a possible replacement in circulating HPV types.

POTENTIAL IMPACT OF HPV IMMUNIZATION ON WOMEN’S SCREENING BEHAVIOURS

An HPV immunization program is expected to reduce the incidence of cervical cancer but will not eradicate the disease. All sexually active women, whether or not they have been immunized, should continue to undergo cervical cancer screening. A coordinated set of interventions must be put in place to maintain and improve adherence to screening procedures (surveys on attitudes and behaviour, various educational interventions, follow-up system, etc.). Immunization and existing cervical cancer prevention programs are complementary, especially in the context of uncertainties regarding duration of vaccine protection.

CIC recommends the development of a national consensus on screening programs. Appropriate studies must be conducted to determine what changes may be required in screening schedules and programs and what new screening tools will need developing as a result of implementation of an HPV immunization program.

In addition to determining the impact of vaccines on cancer screening, any impact on sexual behaviour should also be evaluated.

CIC/NACI WORKING GROUP RECOMMENDATIONS ON PROGRAM EVALUATION

Evaluation of the HPV immunization program will be complex, but it is crucial because of its major impact on the health of women and on screening activities, the amounts of money invested and the need to review future strategies as a function of advances in knowledge.

In parallel with the optimization of the HPV immunization program, CIC recommends developing a detailed evaluation plan. Immunization coverage, and the incidence and prevalence of HPV-associated diseases and cervical cancer will have to be monitored. The efficacy and duration of the protection conferred by the vaccine as well as the psychosocial impact of immunization (for instance, screening adherence in immunized women or the knowledge, attitudes and practices of the public and health professionals) will need evaluation.

The development of optimal cervical cancer screening approaches, including the need to define the role of HPV testing, should be an integral part of HPV immunization program evaluation in order to assess the impact of immunization on HPV infection, cervical cancer and its precursors.

The evaluation of the immunization program will require specific tools. The availability of a registry of HPV immunization coverage and a registry of cervical cancer, as well as a national HPV sentinel surveillance system, will be important components in this evaluation. Effective linkage between the latter databases will be needed.
HPV IMMUNIZATION PROGRAM GOALS, AND RECOMMENDATIONS

In 2007, the HPV immunization program goal was established as decreasing the morbidity and mortality of cervical cancer, its precursors and other HPV-related cancers in women in Canada (79). Details on the goal and related immunization strategies can be found in the 2007 CIC statement (79). At the time, that goal did not consider the HPV-related burden of disease from conditions other than cancer, nor did it consider the immunization of males. The CIC HPV Task Group recognizes that these aspects are important to consider in the implementation of immunization programs and immunization policies. The HPV immunization program goal has been expanded to:

- Reduce vaccine preventable HPV related morbidity and mortality in the Canadian population.

Under the new broader goal, jurisdictions can elect to retain the focus of the 2007 goal with its emphasis on the reduction of morbidity and mortality of cervical cancer, its precursors and other HPV-related cancers in women. The expansion of the goal to reduce vaccine preventable HPV-related morbidity and mortality in the Canadian population also provides the flexibility for HPV immunization to consider other aspects of HPV morbidity. As well, the expanded goal provides flexibility for the inclusion of males and other population subgroups in HPV immunization programs. The expansion of the goal does not imply that HPV immunization programs must be offered to both sexes; rather, consideration should be given to potential or expected health outcomes of any program for both males and females. It also does not imply that programs need to address all HPV-related diseases; rather, consideration should be given to diverse disease states as priority targets.

In support of the new national goal for HPV immunization programs to reduce vaccine preventable HPV related morbidity and mortality in the Canadian population, the CIC makes the following recommendations related to ongoing and new HPV immunization programs:

1. National HPV vaccine coverage rates among immunization program recipients: High uptake of the HPV vaccine among population groups targeted by HPV immunization program is a key to immunization program success in terms of achieving its goal. Thus, it is recommended that measures be taken to improve and optimize HPV vaccine coverage.

2. Evaluation and the setting of indicators: It is recommended that adequate measures be taken to prioritize the evaluation of new and ongoing HPV immunization programs. In order to evaluate the impact of HPV immunization programs on the population in a systematic manner, it is recommended that program indicators be developed and adopted.

3. New and unresolved research priorities: It is recommended that new research priorities be considered to reflect recent findings related to HPV as well as changes in HPV immunization programs in addition to addressing unresolved research priorities.

4. New population groups into immunization programs: It is recommended that the integration of new population groups into HPV immunization programs be considered using a thoughtful risk-based approach examining issues such as equity and ethical considerations, existing immunization schedules, and the impact of HPV immunization programs on cervical cancer screening.
REFERENCES


37. Louchini R, Goggin P, Duarte-Franco E, Steben M, editors. High risk of anal cancer in individuals treated for anal condylomas in a population-based transversal study, Quebec (Canada), 1990 to 1999. Program and abstracts of the 18th International Society for Sexually Transmitted Disease Research (ISSTDR); 2009 June 28-July 1; London, UK.


47. Buckley JD, Harris RW, Doll R, Vessey MP, Williams PT. Case-control study of the husbands of women with dysplasia or carcinoma of the cervix uteri. Lancet. 1981 Nov 7;2(8254):1010-5.


90. Merck Frosst Canada Ltd. GARDASIL - quadrivalent recombinant vaccine against the human papillomavirus (types 6, 11, 16 and 18). Quebec: 2011.


109. Naud P. Sustained immunogenicity and efficacy of the HPV-16/18 vaccine in women aged 15–25 years: follow-up to 9.4 years. 27th International Papillomavirus Conference and Clinical Workshop; Berlin, Germany. September 2011.


148. Gilca V, Sauvageau C, Dionne M, editors. Preliminary safety and immunogenicity data of two doses of Twinrix and Gardasil co-administered or administered separately according to an extended schedule. Poster presentation. 4th Vaccine and ISV Global Congress; 2010 3-5 October Vienna, Austria.


175. Read TR, Hocking JS, Chen MY, Donovan B, Bradshaw CS, Fairley CK. The near disappearance of genital warts in young women 4 years after commencing a national human papillomavirus (HPV) vaccination programme. Sex Transm Infect. 2011 Dec;87(7):544-7.


