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An Advisory Committee Statement (ACS)
National Advisory Committee on Immunization (NACI)†

Update on Human Papillomavirus (HPV) Vaccines

Preamble

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada with ongoing and timely medical, scientific and public health advice relating to immunization. The Public Health Agency of Canada acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of the Public Health Agency of Canada's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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I. Introduction

In July 2006, a quadrivalent human papillomavirus vaccine (HPV4) (Gardasil®, Merck Canada, Inc.) was authorized in Canada for use in females 9 to 26 years of age for the prevention of infection caused by the HPV types 6, 11, 16, and 18 and the following diseases associated with these HPV types:

- Cervical cancer
- Vulvar and vaginal cancers
- Genital warts (condyloma acuminata)
- Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grades 1, 2 and 3
- Vulvar intraepithelial neoplasia (VIN) grades 2 and 3
- Vaginal intraepithelial neoplasia (VaIN) grades 2 and 3

In February 2010, Gardasil® was authorized to expand its indications to include males 9 to 26 years of age for the prevention of infection caused by HPV types 6, 11, 16, and 18 and for genital warts (condyloma acuminata) caused by HPV types 6 and 11. [1]

In April 2011, Gardasil® was approved for use in women up to the age of 45 years.

In May 2011, Gardasil® was indicated in females and males 9 through 26 years of age for the prevention of:

- 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.

Also in February 2010, a bivalent HPV vaccine (HPV2), Cervarix™ (GlaxoSmithKline Inc.), was authorized for use in Canada in females 10 through 25 years of age. Cervarix™ is indicated for the prevention of cervical cancer by protecting against the following dysplastic lesions caused by oncogenic HPV types 16 and 18:[2]

- CIN grades 1, 2 and 3
- Cervical AIS

This statement will:

- Review existing National Advisory Committee on Immunization (NACI) recommendations on HPV vaccines;
- Review the epidemiology of HPV among females and males, including the burden of anogenital warts and HPV-associated cancers;
- Provide information on the HPV2 (Cervarix™) vaccine and recommendations for its use;
- Provide updated information on the use of HPV4 (Gardasil®) vaccine and new information specific to its use in males.

Overview of past National Advisory Committee on Immunization recommendations for HPV vaccine

NACI issued a statement in 2007[3] recommending the use of HPV4 in:

- Females between 9 and 13 years of age
- Females between the ages of 14 and 26 years (even if they are already sexually active, with or without previous Papanicolaou test (Pap) abnormalities, including cervical cancer, or have had genital warts or known HPV infection).

For females >26 years of age, studies of Gardasil® vaccine use were ongoing at the time of publication in 2007. It was noted in the previous statement that use of the vaccine in females >26 years of age could be considered in individual circumstances.

II. Methods

In brief, the broad stages in the preparation of a NACI statement are:

1. knowledge synthesis (retrieve and summarize individual studies, rank the level and quality of the evidence)
2. synthesis of the body of evidence of benefits and harms, considering the quality of the evidence and magnitude of effects observed
3. translation of evidence into a recommendation.

Further details regarding this process are outlined in: *Evidence-Based Recommendations for Immunization: Methods of the NACI, January 2009, CCDR* at: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/acs-1/index-eng.php).

NACI reviewed the draft work plan of the HPV Working Group and the key questions for the proposed literature review, including such considerations as the burden of illness of the disease to be prevented and the target populations, safety, immunogenicity, efficacy, effectiveness of the vaccines, vaccine schedules, and other aspects of the overall immunization strategy. The knowledge syntheses were performed by Dr. Meena Dawar, Community Medicine Specialist, Tara Harris, Senior Nurse Epidemiologist with the Public Health Agency of Canada, and Dr. Shelly McNeil, Infectious Diseases Specialist, and supervised by the Working Group. Following critical appraisal of individual studies, summary tables with ratings of the quality of the evidence using NACI's methodological hierarchy (Table 17) were prepared, and proposed recommendations for vaccine use were developed. The Working Group Chairperson and a PHAC Medical Specialist presented the evidence and proposed recommendations to NACI on October 6, 2010. Following thorough review of the evidence and consultation at the NACI meeting of October, 2010, the committee voted on specific recommendations. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the text.

III. Epidemiology

III.1. Females

HPV epidemiology in females was reviewed extensively in the 2007 NACI HPV statement.[3] Relevant data since that statement are summarized here.

A study by Moore *et al*. estimates HPV prevalence among females, using the largest Canadian population-based sample to date[4]. Prevalence and type distribution of HPV DNA was determined from a sample (n=4821) of women aged 13 to 86 years participating in the provincial cervical cancer screening program in British Columbia (BC). 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: 3.7-0.1-0.4.8), 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). These overall prevalence estimates are comparable to other studies.

In a seroprevalence study based on a sample of 1020 age-stratified anonymous sera from women 15 to 39 years of age in BC undergoing prenatal testing,[5] HPV type 16 and 18 antibodies were detected in 17.9% and 9.5% of subjects respectively, and 3.9% had antibodies to both types. Based on age-stratified data, the authors concluded that exposure to HPV types 16 and 18 occurred at a young age. The neutralizing antibody titres were maintained across all age groups, which could possibly be due to persistent infection, re-infection, or long-term antibody persistence.

The peak risk for HPV infection is within the first five to ten years of the first sexual experience. A recent meta-analysis of over 44 studies worldwide indicates that a second peak in HPV infection prevalence occurs in women ≥45 years of age in all regions with the exception of Asia, where rates

continue to decline beyond 45 years of age.[6] The magnitude of the second peak is reduced compared to peak rates in younger women. In a cohort of 1610 Colombian women, the five-year cumulative risk of cervical HPV infection, defined by the presence of HPV DNA, of any type was 22.0% for those aged 30 to 44 years and 12.5% for those aged ≥45 years compared to 42.5% among those 15 to 19 years of age.[7] Possible explanations for the second peak of HPV infection include reactivation of latent infection, new infections because of age-related social or behavioral change, or a cohort effect. The extent to which infections occurring in later life are associated with subsequent risk of cancer and pre-cancer is not yet known.

III.2. Males

HPV epidemiology was reviewed extensively in the 2007 NACI HPV statement.[3] While there are limited data on the natural history, epidemiology and burden of HPV-related disease in males, several studies have been published since the 2007 statement and additional studies are ongoing.[8] Relevant data on HPV epidemiology in males since that statement are summarized here, in particular anogenital warts and HPV-associated cancers in men.

Natural history of HPV infection in males

Similar to females, most HPV infections in males are asymptomatic. Anogenital warts (AGW) are attributable to HPV types 6 and 11 in most cases (>90%) and 20-50% of cases involve co-infection with oncogenic HPV types.[8-10]

HPV causes both benign and malignant anogenital disease and head and neck lesions. HPV types 16 and 18, which are also referred to as high-risk (HR) types, are associated with cancers of the penis, anus,[11] mouth and oropharynx.

Mechanisms of oncogenicity in HPV-associated cancers affecting men, and non-cervical HPV-associated cancers in women, are incompletely understood, but presumed to be similar to those of the cervix. For example, about 90% of anal squamous cell cancer is associated with HPV and arises in the transformation zone, a region pathologically similar to that of the cervix where the squamous epithelium meets the columnar epithelium. Anal cancer is believed to be preceded by anal intraepithelial neoplasia (AIN) II or III.[11]

Prevalence and incidence of HPV infection in males

HPV is not a notifiable disease in Canada. Estimates of HPV infection and associated disease burden among males are primarily based on prevalence and incidence studies in selected populations, many of which may have a bias towards higher rates of infection because of multiple sexual partners. Data of disease burden are needed to understand the epidemiology of infection and to assess the potential impact of immunization programs. 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 *versus* multiple sites), use of different analytical methods, and the selection criteria of the populations studied.[8]

A systematic review of over 40 studies by Dunne *et al*. reports prevalence estimates between 1.3% and 72.9% among studies assessing multiple sites, with 56% of studies reporting a prevalence of ≥20%.[12] HPV type 16 is consistently among the most common types reported.

The HPV in Men (HIM) study is an ongoing study to assess a variety of aspects of HPV infection among men aged 18 years and older recruited from three different countries (Brazil, Mexico and the United States) using a common protocol for sampling and HPV detection. An overall prevalence of 65.2% has been observed in this study population (n=1160). Overall prevalence was higher in Brazil (72.3%) than in the United States (US) (61.3%) and Mexico (61.9%). Multiple types were detected in 25.7% of all participants, while 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%).[13]

There are few published Canadian studies of HPV prevalence or incidence among men. Ogilvie *et al*. reported a prevalence of any HPV type from any site (glans penis/foreskin, penile shaft and scrotum were sampled) of 69.8% in a sexually transmitted infection (STI) clinic population of heterosexual males in Vancouver, BC.[14]

Seroprevalence studies can assist in understanding epidemiology of infection, and cumulative exposure over time and has been assessed in a limited number of studies in males.[15-17] Two population-based studies from Australia and the US have been recently published. A large population-based sample of Australians 0 to 69 years of age showed

overall seroprevalence of HPV was significantly higher among women (23.8%; 95% CI: 21.8-25.8) compared to men (17.8% [%; 95% CI: 15.7-20.0]), consistent with previous studies. Among males, type-specific seropositivity varied by age with peaks observed at ages 40 to 49 years for types 6 and 11 (15.4% and 9.1% respectively) and 50 to 59 years for types 16 and 18 (14.3% and 8.2% respectively).[18] The peaks occurred approximately ten years later among males than among females. Population-based estimates of HPV seroprevalence from the US, based on the 2003-2004 National Health and Nutrition Examination Survey (NHANES),[19] showed overall HPV seroprevalence among males 14 to 59 years (N=2128) of 12.2%. This was considerably lower than for females (32.5%), as observed elsewhere.[12, 16, 17, 20, 21] The authors suggest that lower seroprevalence among males is likely due to differences in the immune response induced by HPV infection among males, rather than lower infection rates.[19]

Large population-based studies on incidence of HPV infection in males over time are not available. In a prospective cohort study of 290 American men aged 18 to 44 years, the cumulative incidence of new infection over 12 months was 29.2% and 42.3% for any HPV infection. Type-specific incidence was estimated at 2.8, 0.5, 4.8 and 0.8 per 1000 person-months for HPV types 6, 11, 16 and 18, respectively.[22] In another study of 290 male university students, cumulative incidence of any HPV infection over 24 months was 62.4%.[23]

Risk factors for HPV in males

The most consistent factor associated with increased risk of acquisition of HPV infection among males is the lifetime number of sex partners.[24-26] In Lu *et al.*, men reporting ≥ 16 lifetime sex partners compared to those with zero to four lifetime partners, had an elevated risk of any HPV infection (adjusted hazard ratio [AHR]=2.8; 95% CI: 1.1-7.1), of oncogenic HPV infection (AHR=9.6; 95% CI: 2.4-37.8), and non-oncogenic HPV infection (AHR=3.6; 95% CI: 1.3-9.9). A significant protective effect associated with circumcision is reliably reported in the literature.[23-27]

In a recent randomized-controlled trial on circumcision conducted by Auvert and colleagues in South Africa, high-risk HPV was identified in 14.8% of circumcised men and 22.3% of uncircumcised men (control group) (adjusted rate ratio=0.68; 95% CI: 0.52-0.89).[27] Nielson *et al.* report 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).[28] No significant association between age and HPV prevalence, incidence or duration of infection has been found.[13, 22]

Anogenital warts (AGW) in men and women

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. Both Kleiwer *et al*. [29] and Marra *et al.* [30] link population-based hospital and physician databases to estimate the incidence and prevalence of AGW, in Manitoba and BC respectively. Marra *et al.* present additional data with respect to burden of illness and costs.[30]

Both studies report 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) and 131 per 100 000 in men and 121 per 100 000 in women (BC, 2006). 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 and incidence peaked between 20 and 24 years of age for women and 25 to 29 years of age for men.

Twenty-year time trend analysis in Manitoba shows a peak in AGW incidence in 1992 followed by a decline, with slightly increasing rates in recent years, particularly among men. The male:female incidence rate ratio has increased over time from 0.76 in 1985 to 1.25 in 2004.[29]

In BC, the mean length of episode of AGW is estimated at 69 days (2.5 months) with the average length of 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 estimated annual, direct medical costs in BC of approximately $C1 million.[30]

Similar estimates of AGW prevalence (130 per 100 000) are reported in the United Kingdom, where AGW is a reportable disease.[31] Estimates from the US are slightly higher, between 150 and 205 per 100 000 in privately-insured populations.[32-34] Cumulative prevalence (self-reported diagnosis with AGWs by a health practitioner) of 5.6% among 18 to 59 year olds is estimated from the US NHANES.[35]

In addition to the direct health impact, AGW are also shown to have significant impact on quality of life. A study by Marra *et al*. used standardized questionnaires to assess health-related quality of life (HRQoL) among 75 subjects in Vancouver, BC, with a history of AGW.[36] Low HRQoL associated with AGW was found which was substantial and comparable in magnitude to some well-delineated chronic diseases such as genital herpes. A recent abstract presented by Drolet *et al*. reported HRQoL in 131 individuals with new AGW diagnoses. HRQoL measures were converted into utility scores for quality-adjusted life year (QALY) estimation. Preliminary results suggest a first episode of AGW produces a QALY loss equivalent to 9 to 40 days of healthy life lost.[37]

HPV-related cancers in men

The total burden of HPV-associated cancers among both genders is estimated at 5.2% of all cancers worldwide.[38] The International Agency for Research on Cancer (IARC) has conducted an assessment of carcinogenicity of human papillomaviruses. The 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 squamous cell carcinoma of the larynx and with uncommon Buschke-Löwenstein tumours of the penis, and anus.[39]

Among cancers affecting men, it is estimated that HPV infection is associated with 80-90% of anal cancers, 40-50% penile, 35% oropharyngeal and 25% of oral cavity cancers.[38, 40-42] 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.[38]

The following annual incidence rates of male HPV-associated cancers are estimated using the Public Health Agency of Canada's Cancer Surveillance On-line tool, which provides aggregated data from provincial and territorial cancer registries and the Health Statistics Division of Statistics Canada.[43]

Table 1: Average annual number of cases and age-standardized incidence of HPV-associated cancers among persons aged 15 years and older in Canada (1997-2006) and estimated attributable proportion due to HPV.

Sex	Anatomical site*	Average annual incidence (per 100 000)[43]	Average annual number of cases	Estimated attributable proportion (%)[38, 41, 42]	
				Any HPV type	HPV types 16 and 18 (% of all HPV types)
Males	Penis	1.0	127.4	50	63
	Anus	1.6	208.2	90	92
	Oral cavity	6.5	853.1	25	89
	Oropharynx	0.64	84.3	35	89
Females	Cervix	10.1	1356.8	100	70
	Vagina and vulva	4.2	651.8	40	80
	Anus	1.7	267.0	90	92
	Oral cavity	3.3	501.2	25	89
	Oropharynx	0.18	27.2	35	89

***** Anatomical site is based on the International Classification of Diseases for Oncology Third Edition (ICD-O-3) list of causes, with the exception of oral cavity which includes cancers of the "floor of the mouth", "gum and other mouth" and "tongue").[43]

Similar estimates of incidence are obtained from population-based cancer registry data in the US. The average annual incidences of male HPV-associated cancers are estimated at 7.0 per 100 000; 5.2 per 100 000 for oral cavity/oropharyngeal cancers, 1.0 per 100 000 for anal cancers and 0.8 for penile cancers.[40]

Anal cancer

In 2006 (the most recent year for which national data is available), the incidence of anal cancer among males (≥15 years of age) in Canada was 1.5 per 100 000 (222 cases). Although men have slightly lower rates of anal cancer than women, both Canadian and US data indicate that the overall incidence of anal cancer has increased for both females and males over the past several decades.[43, 44] In the US, between 1973 and 2000, twice the rate of increase was observed among men (160%) compared to women (78%). In addition to HPV, anal cancer among males is associated with lifetime number of sexual partners, receptive anal intercourse, human immunodeficiency virus (HIV) infection and cigarette smoking.[45]

Overall, five-year survival from anal cancer decreases with advancing stage of disease, and males have lower survival overall compared to females for all stages of disease.[44, 45] A Quebec study reported that five-year survival probability for men with anal cancer decreased from 57% in 1984 to 46% in 1995, and survival of females with anal cancer increased from 56% to 65%.[46] Using data obtained from SEER (Surveillance, Epidemiology and End Results), a population-based tumour registry in the United States, Johnson *et al*. report a relative five-year survival of 58% compared to 64% for women. Among those with localized disease, survival at five years after diagnosis is 78%, compared to 56% of those with regional-stage disease and 18% with distant disease.[44, 45]

Penile cancer

Penile cancer is rare, representing less than 1% of all male cancers.[38] The rate of penile cancer in Canada in 2005 was 0.68 per 100 000 (119 cases).[43] Rates increase steadily with age. Aside from HPV infection, risk factors associated with penile cancer include smoking, lack of circumcision, phimosis, chronic penile inflammation and immunosuppression.[47, 48] There is also wide variation in incidence observed internationally and between ethnic groups which may be related in part to circumcision status.[38, 48] Circumcision is associated with a three-fold reduction in risk of penile cancer.[49, 50] Similar to anal cancer, Louchini *et al*. find that in Quebec, survival probability following penile cancer diagnosis has decreased from 75% in 1984 to 59% in 1995.[46]

Oropharyngeal and oral cavity cancers

In 2005, the incidence of cancers of the oropharynx and oral cavity among men in Canada was 0.54 per 100 000 and 5.2 per 100 000 respectively.[43]

While most cancers of the pharynx and oral cavity are associated with tobacco and alcohol use, recent evidence supports an association between HPV infection and a subset of these cancers.[51] Anatomic sites specifically associated with HPV-associated oral cancers include the base of the tongue, Waldeyer ring, lingual and palatine tonsils and the oropharynx.[47] A systematic review of over 60 studies by Kreimer *et al.* reports HPV-DNA detection in 26% of all squamous cell carcinomas (SCCs) of the head and neck (35.6% of oropharyngeal SCCs, 23.5% of oral SCCs and 24.0 of laryngeal SCCs).[41] HPV type 16 was the most common type detected accounting for 86.7%, 68.2% and 69.2% of all HPV positive oropharyngeal, oral and laryngeal SCCs respectively.[51] Among cancers of the oropharynx and oral cavity, tonsillar squamous cell carcinoma is the most strongly and consistently associated with HPV type 16 infection.[51]

Relationship between 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.[52] 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.[53-56]

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). Three recent studies report increases in anal cancer among HIV-infected MSM.[55, 57, 58] D'Souza *et al*. [57] reports a 4.6-fold increase in the incidence of anal cancer among HIV-positive men in the HAART era (1996-2006; 137 per 100 000 person-years; 95% CI: 84-224) compared with the pre-HAART era (1984-1995; 30 per 100 000 person-years; 95% CI: 13-66). Rates of anal cancer among HIV-positive men 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.[59]

Contribution of male HPV infection to female infection and disease

Sex with HPV infected males is associated with increased risk of precancerous lesions and cervical cancer in women.[60-66] 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 is observed among women whose partners tested positive for the presence of HPV DNA (adjusted OR=4.9; 95% CI: 1.9-12.6).[61] Risk of cervical cancer is also significantly associated with lack of circumcision in male partners, which is known to significantly increase the risk of HPV infection. In a study by Castellsague *et al*., monogamous women whose male partners had at least six sexual partners and were circumcised had a lower risk of cervical cancer compared to those with uncircumcised partners who had had at least six sexual partners (adjusted OR=0.42; 95% CI: 0.23-0.79).[63]

A recent 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.[67] Burchell *et al.* assessed participants of the HITCH (HPV Infection and Transmission among Couples through Heterosexual activity) study whose primary subjects are women attending university or college in Montreal, Quebec and their partners. Overall, among 263 couples, prevalence of HPV infection was 56% with higher prevalence among those with infected partners (83%) compared to those whose partners were not infected (19%). 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.[68]

There are currently no 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.[69] Modeling studies have assessed the impact of HPV immunization of males with varying results. A transmission dynamic model by Elbasha *et al.* predicts that while a quadrivalent HPV vaccine program vaccinating 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 further reduction with a resulting total decrease of 97% for anogenital warts and 91% for cervical cancer.[70] Another transmission-based dynamic model to assess cost-effectiveness of quadrivalent HPV vaccine in Mexico determined that a strategy that includes immunization of 12 year olds (both male and female) plus a temporary catch-up program for 12 to 24 year olds (both sexes) further expands the number of HPV disease cases prevented by over 30% (800 000 additional cases) and cervical cancer deaths avoided by 23% (1165 additional deaths prevented) compared to a female-only strategy.[71]

Two models predict the impact of vaccination on HPV type 16 infections and cervical cancer, respectively. The first model predicts that vaccination of 80% of 12-year old girls in Australia will eventually reduce HPV type 16 prevalence by 60 to 100% in vaccinated and 7 to 31% in unvaccinated females whereas if 80% of boys are also vaccinated, reductions will be 74 to 100% in vaccinated and 86 to 96% in unvaccinated females.[72] The second model explores the optimal age at vaccination and pattern of vaccine introduction in Finland.[73] The authors find that, once the full impact of vaccination is reached, the annual proportion of HPV type 16-associated cervical cancer cases prevented is expected to be 67% if vaccination of girls occurs at age 15 years, and/or 68% if it occurs at age 12 years, assuming 70% coverage. If vaccination occurs at age 12 years, vaccinating males as well as females is found to prevent an additional 15% of cases annually, if male coverage is 30%.

Two additional models are based upon roll-out of bivalent HPV type 16/18 vaccine. Taira *et al*. predict that inclusion of males into a 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.[74] A cost-effectiveness analysis by Kim *et al*. found that including males in a bivalent HPV vaccine program provided an additional 4% cancer reduction beyond a reduction of 63% predicted for females alone.[75]

III.3. Summary of HPV immunization programs in Canada

Since the fall of 2008, all provinces and territories have introduced/announced HPV immunization programs for pre-adolescent/adolescent girls into their routine immunization schedules. All programs include females only.

Table 2: Human papillomavirus immunization programs by province/territory (September 2010).

Province/Territory	Routine Schedule (0, 2 and 6 months)	Date of Implementation of Routine Program	Catch-up Programs (Date of Implementation)
British Columbia	Grade 6	September 2008	Grade 9 (2008-2011)
Alberta	Grade 5	September 2008	Grade 9 (2009-2012)
Saskatchewan	Grade 6	September 2008	Grade 7 (2008-2009)
Manitoba	Grade 6	September 2008	
Ontario	Grade 8	September 2007	
Quebec	Grade 4 (doses 1 and 2), in 3rd year of secondary school (dose 3)	September 2008	9 to13 years of age (High Risk of HPV Infections) 14-17 years of age 9 to 17 years of age in First Nations communities 3rd year of secondary school (2008-2013)
New Brunswick	Grade 7	September 2008	Grade 8 (2008-2009)
Nova Scotia	Grade 7	September 2007	Grade 10 (2009-2010 only) Grade 8 (2010-2011 only)
Prince Edward Island	Grade 6	September 2007	Grade 9 (2009-2010 only)
Newfoundland and Labrador	Grade 6	September 2007	Grade 9 (2008-2010)
Northwest Territories	Grade 4	September 2009	Grades 11 and 12 (2009-2010) Grades 10 and 11 (2010-2011) Grades 9 and 10 (2011-2012) Grade 9 (2012-2014)
Yukon	Grade 6	September 2009	Grades 7 and 8
Nunavut	Grade 6	March 2010	

IV. Vaccine

IV.1. Preparations authorized for use in Canada

HPV4

The quadrivalent HPV vaccine, Gardasil®, consists of the L1 capsid protein of each of four HPV strains (types 6, 11, 16 and 18). A gene encoding the L1 protein of each type is expressed in the yeast *Saccharomyces cerevisiae*. The protein product self-assembles into a non-infectious virus-like particle (VLP) that is similar to the natural virus, but no viral genome is present. The vaccine is administered as a 0.5 mL dose, which contains the following:

- HPV type 6: 20 µg L1 protein
- HPV type 11: 40 µg L1 protein
- HPV type 16: 40 µg L1 protein
- HPV type 18: 20 µg L1 protein

The VLPs of each type are purified and adsorbed onto an aluminum-containing adjuvant (amorphous aluminum hydroxyphosphate sulfate 225 µg). The formulation also includes sodium chloride, L-histidine, polysorbate 80, sodium borate and water for injection. The product does not contain preservative or antibiotics, and the packaging is latex-free.[3]

HPV2

The bivalent HPV vaccine, Cervarix™, consists of L1 capsid proteins of two HPV genotypes, HPV type 16 and HPV type 18. These L1 proteins are expressed using a baculovirus expression system which contains two components: an insect producer cell line from *Trichoplusia ni* Hi-5 and a baculovirus strain genetically engineered to carry the L1 gene.[76] The protein product self-assembles into an empty virus-like particle (VLP) that is similar to the natural virus, but no viral genome is present. Cervarix™ is administered as a 0.5 mL dose and contains the following:

- HPV type 16: 20 µg L1 protein
- HPV type 18: 20 µg L1 protein

HPV2 contains a novel proprietary adjuvant, AS04, which consists of 500 µg of aluminum hydroxide and 50 µg of 3-O-desacyl-4'-monophosphoryl lipid A (MPL). MPL is a deactivated derivate of lipopolysaccharide from the cell wall of *Salmonella minnesota*, a bacteria that is ubiquitously present in the environment. AS04 works on the innate and adaptive immune pathways. Stimulation of innate immunity by activation of toll-like receptor-4[77] and induction of high levels of tumor necrosis factor-α (TNFα)[78] have been demonstrated. In comparison to aluminum hydroxide, AS04 also induces a stronger adaptive immune response with higher antibody levels and genotype specific memory B cells following vaccination.[78] AS04 is present in two other GSK vaccines: Fendrix™, a hepatitis B vaccine for hemodialysis patients licensed in the European Union and a genital herpes simplex virus (HSV) candidate vaccine which is no longer being evaluated. Over 40 000 doses of AS04 have been administered in trials of these two vaccine products, and an additional 19 000 doses have been administered in the conduct of the bivalent HPV vaccine trial.[79, 80] The vaccine formulation also includes 4.4 mg sodium chloride, 623 µg sodium dihydrogen phosphate dehydrate, and water for injections.[2]

IV.2. Vaccine efficacy

Table 18 contains the evidence tables summarizing the individual studies cited here.

HPV quadrivalent vaccine (HPV4): Gardasil®

Efficacy of HPV4 in females 16-26 years of age

The efficacy of Gardasil® in females aged 16 to 26 years has been evaluated in four Phase II and III clinical trials and this data was presented in detail in the 2007 NACI Statement. Overall, prevention of HPV type 16 and HPV type 18-related cervical cancer surrogates (CIN 2/3, or AIS) was 100% (95% CI: 93-100) in the per protocol efficacy (PPE) analyses of these studies and 99% (95% CI: 93-100) in the HPV-naive modified intention-to-treat (ITT) analysis. In the combined data set from Phase II and III studies, efficacy against external genital lesions (EGL) related to HPV types 6, 11, 16, or 18, including warts, and to VIN and VaIN was 99% (95% CI: 95-100) in the PPE and 95% in the modified intention-to-treat analysis (95% CI: 90-98).[3]

Since the publication of the 2007 NACI statement, data on the impact of HPV4 on rates of Pap test abnormalities and cervical procedures have been published.[81] Among HPV-naive women (seronegative and polymerase chain reaction (PCR)-negative to 14 high-risk HPV types) aged 15-26 years enrolled in the FUTURE I and FUTURE II trials with a mean follow-up of 3.6 years, vaccination with HPV4 resulted in an overall reduction in abnormal Pap tests of 17.1%, irrespective of HPV type (reduction in colposcopy of 19.8%, reduction in cervical biopsy of 22%, and reduction in cervical definitive therapy of 42.3%). This study population is likely most representative of the adolescent population in Canada immunized in school-based programs. Among women in the ITT population in the FUTURE I and II studies, a population more representative of the sexually active population, statistically significant reductions were observed in abnormal Pap tests (11.3%; 95% CI: 6.5-15.9), cervical definitive therapy (23.0%; 95% CI: 14.2-31), and procedures for external genital lesions (28.3%; 95% CI: 14.5-45), irrespective of HPV type.

Additional data has also become available on the efficacy of HPV4 in the prevention of new CIN2 or worse in women who have previously undergone therapy for HPV-related cervical abnormalities.[81] Joura *et al*. recently reported the results of a secondary analysis of the FUTURE I[82] and FUTURE II[84] studies evaluating the efficacy of this vaccine in women aged 16 to 26 years who had previously undergone definitive treatment for cervical disease (Loop Electrosurgical Excision Procedure (LEEP) or conization) (n=1350) or genital warts, VIN, or VaIN (n=704). Among women previously treated for cervical disease, vaccination with HPV4 was associated with a reduction in the incidence of new CIN2+ disease due to any HPV type of 65% (95% CI: 20-86) and of genital warts, vulvar intraepithelial neoplasia (VIN) or vaginal intraepithelial neoplasia (VaIN) due to any HPV type of 47% (95% CI: 4-71). Among women with a history of anogenital warts, VIN, or VaIN, there was a non-statistically significant trend toward reduction in the incidence of new CIN2+ diseases due to any HPV type of 41% (95% CI: -15-71) and of AGW, VIN, or VaIN of 23% (95% CI: -12-48) associated with HPV4 vaccination.

Efficacy of HPV4 in females >26 years of age

Efficacy of HPV4 in females 24 to 45 years of age (n=3819) was studied in a randomized, double blind, placebo controlled trial at 38 international sites, from which 2.2 year (of four year) follow-up data is available.[85] Analysis was undertaken in the population who followed the study protocol exactly (per-protocol/PPE population) along with two additional populations: naive to the relevant type (NRT) and ITT populations (see Table 3 below for definitions). The co-primary (composite) end-point was defined as incidence of infection of at least six-month duration and cervical and external genital disease (including cervical, vulvar, or vaginal intraepithelial neoplasia; adenocarcinoma *in situ*; cervical, vulvar or vaginal cancer; and genital warts).

Efficacy against the co-primary end-point in the PPE population was 90.5% (95% CI: 73.7-97.5) for HPV types 6/11/16/18 and 83.1% (95% CI: 50.6-95.8) for types 16/18 only. Efficacy against the co-primary end-point in the ITT population was 30.9% (95% CI: 11.1-46.5) and 22.6% (95% CI: -2.9-41.9) for HPV 6/11/16/18 and types 16/18 respectively. (Table 3).

Table 3: Efficacy of HPV4 vaccine (Gardasil®) against the combined incidence of vaccine-type-related infection of at least six-month duration, cervical intraepithelial neoplasia, and external genital lesions in females 24 to 45 years of age (n=3819).[85]

	Vaccine (n=1910)			Placebo (n=1907)			Efficacy (%) (95% CI)	p value
	N	Cases	Rate‡	n	Cases	Rate		
Per-protocol population (PPE)*								
HPV types 6/11/16/18	1615	4	0.1	1607	41	1.5	90.5 (73.7-97.5)	<0.0001
HPV types 16/18	1601	4	0.1	1579	23	0.9	83.1 (50.6-95.8)	0.0001
Naive to relevant type population (NRT)**								
HPV types 6/11/16/18	1841	20	0.5	1833	77	2.0	74.6 (58.1-85.3)	
HPV types 16/18	1823	14	0.4	1803	48	1.2	71.6 (47.6-85.5)	
Intention to treat population (ITT)†								
HPV types 6/11/16/18	1886	108	2.7	1883	154	3.9	30.9 (11.1-46.5)	
HPV types 16/18	1886	90	2.2	1883	115	2.9	22.6 (-2.9-41.9)	

* The per-protocol population (PPE) included participants who were seronegative to the relevant HPV type at day 1, PCR negative to that type in cervicovaginal swabs or biopsy samples from day 1 until month 7, received all three vaccinations within one year and had ≥1 follow-up visit after month 7.

** The naive to relevant type population (NRT) was a modified PPE that included women who were naive to a vaccine HPV type at day 1 (by both PCR and serology), received ≥1 dose of vaccine or placebo and had ≥1 follow-up visit after day 1.

† The intention to treat population (ITT) included all women who received ≥1dose of vaccine or placebo and had ≥1 follow-up visits after day one (including protocol violators and those with preexisting HPV infections).

‡Rate = incidence rate per 100 000 persons years at risk

Efficacy of HPV4 against oncogenic HPV genotypes not included in the vaccine

A total of eighteen HPV types are considered oncogenic based upon epidemiologic and/or genetic evidence. While HPV types 16 and 18 contribute to 70% of all invasive cervical cancers, oncogenic types belonging to the A7 (18, 39, 45, and 59) and A9 (16, 31, 33, 35, 52 and 58) species other than types 16 and 18 are responsible for up to 20% of all cervical cancers as well as a large proportion of high and low-grade cervical lesions. In a study combining databases from two randomized controlled clinical trials (n=17, 622) by Brown *et al.*[86] vaccination of generally HPV-naive women ages 16 to 26 years with HPV4 (Gardasil®) resulted in a significant reduction in the incidence of HPV type 31/45 infection (which are the most common oncogenic types after 16 and 18) and HPV type 31/45-associated CIN1-3/AIS (cervical intraepithelial neoplasia of any grade/ adenocarcinoma *in situ*) of 40.3% (95% CI: 13.9-59.0) and 43.6% (95% CI: 12.9-64.1) respectively after 3.6 years of follow-up. Efficacy for CIN2-3/AIS associated with 10 non-vaccine types (31/33/35/39/45/51/52/56/58/59) was 32.5% (95% CI: 6.0-51.9). A similar study done by Wheeler *et al.*, [87] using the same trial data as above but including both HPV-naive women and women with preexisting HPV infection and/or HPV-related disease at enrolment, reported a significant reduction in the rate of HPV types 31, 33, 45, 52 and 58 infection of 17.7% (95% CI: 5.1-28.7) and CIN1-3/ AIS caused by those types of 18.8% (95% CI: 7.4-28.9) as a result of vaccination. Reduction in the rate of HPV type 31, 58, 59-related CIN1-3/AIS of 26.0% (95% CI: 6.7-41.4), 28.1% (95% CI: 5.3-45.6) and 37.6% (95% CI: 6.0-59.1) respectively was also shown.

Efficacy of HPV4 in males

A recent randomized, double-blind, placebo controlled trial[88] to assess efficacy, immunogenicity and safety of Gardasil® in males included 4065 young men 16 to 26 years of age, of which 602 self-declared as having sex with men (MSM) (n=602). Participants were administered quadrivalent HPV vaccine or placebo at enrolment, month 2 and month 6 and were followed for a total of 36 months. Primary efficacy analysis was performed in a per-protocol population seronegative at day 1 and PCR negative at day 1 and month 7 to the relevant HPV type. HPV4 was effective against incident and persistent HPV infection with types 6/11/16/18 as well as in reducing the incidence of HPV-related external genital lesions in the study population (Table 4).[88] Efficacy of Gardasil® in males 9 to 15 years of age is inferred by a pre-licensure immunobridging study (Protocol 016) published by Block *et al.*, demonstrating non-inferiority of immune response compared to females 16 to 26 years, as well as analysis conducted by Merck which combines results from both pre-licensure and a male-only trial.[89, 90] (See *Immunogenicity*)

Table 4: Efficacy of HPV4 vaccine in the Per Protocol Population against HPV-related genital infection and disease in young men 16-26 years of age (n=4065) at 2.9 years median follow-up.[88]

Endpoint	HPV4 Gardasil® (n=1397)	Placebo‡ (n=1408)	Efficacy (%)	95% CI	p value
	Cases	Cases			
All external genital lesions (EGL)*	3	31	90.4 (All types) 84.3 (type 6) 90.9 (type 11) 100 (type 16) 100 (type 18)	69.2-97.9 46.5-97.0 37.7-99.8 0-100 0-100	<0.001
Condyloma	3	28	89.4	65.5-97.9	
Penile/perianal/perineal intraepithelial neoplasia (PPPIN)	0	3	100	0-100	
Persistent infection (HPV types 6, 11, 16, 18-related)** HPV type 6-related HPV type 11-related HPV type 16-related HPV type 18-related	15 4 1 9 1	101 33 15 41 25	85.6 88.0 93.4 78.7 96.0	73.4-92.9 66.3-96.9 56.8-99.8 55.5-90.0 75.6-99.9	<0.001
DNA detection†	136	241	44.7	31.5-55.6	<0.001

* EGLs include condyloma (external genital warts), penile/perianal/perineal intraepithelial neoplasia (PIN), penile/perianal/perineal cancer; case counting began after month 7

** HPV DNA detection in anogenital specimens from ≥2 consecutive visits ≥6 months apart (±1 month visit windows) or HPV type 6/11/16/18-related disease with positivity to the same type at adjacent visit

† HPV DNA detection in anogenital specimens from ≥1 visit

‡ AAHS (amorphous aluminum hydroxyphosphate sulfate) placebo

Vaccine efficacy among heterosexual males (n=3463) and MSM (n=602) is also reported.(91) Vaccine efficacy against HPV type 6/11/16/18-related EGL among heterosexual males and MSM was 92.4% (95% CI: 69.6-99.1) and 79.0% (95% CI: -87.9-99.6) respectively; and 83.7% (95% CI: 71.1-91.5) and 94.4% (95% CI: 64.4-99.9) respectively for HPV type 6/11/16/18-persistent infection. Among the MSM population, vaccine efficacy for the primary composite endpoint of HPV type 6, 11, 16, 18-related any grade anal intraepithelial neoplasia (AIN) and anal cancer was 77.5% (95% CI: 39.6-93.3). Efficacy was 74.9% (95% CI: 8.8-95.4) for grade 2 or higher HPV type 6/11/16/18-related AIN and 86.6% (95% CI: 0.013-100) for HPV type 16/18-related AIN. There were no cases of invasive anal cancer in the study.[92, 93]

Post marketing surveillance

Australia introduced a quadrivalent HPV vaccination program for all females age 12 through 26 years in 2007, accompanied by a national sentinel surveillance program for genital warts; coverage is estimated at about 65%. A 59% decline in number of diagnoses for genital warts in female residents ≤26 years was observed, but no change was observed for women older than 26 years, for female non-residents, or for men who have sex with men. Proportionally fewer heterosexual men were diagnosed with genital warts since 2007 (28%).[94]

Indirect protection

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. The Australian surveillance data suggests that vaccination of females may affect transmission to males (see above). Preliminary findings from an analysis of vaccination status among the HPV Infection Transmission in Couples through Heterosexual Activity (HITCH) study suggest that female vaccination prevents transmission to men. In this analysis, a 2.7 fold protective effect against infection among male partners was shown (OR=0.37; 95% CI: 0.083-1.6) although confirmation using a larger sample will be required due to inadequate precision around the estimate.[95]

Hypothetical 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, based on assumptions about transmission of HPV from males to females.[69]

HPV bivalent vaccine (HPV2): Cervarix™ efficacy

Efficacy of HPV2 in females 15-25 years of age

Efficacy data are available for females 15 to 25 years of age who have participated in phase II and III trials of this vaccine. Two phase II[96-98] and two phase III trials[99-101] of HPV2 efficacy had as primary outcomes HPV type16/18-incident infection (phase II) and HPV type 16/18-cervical intraepithelial neoplasia, grade 2 or higher (phase III). The two phase III trials include PATRICIA, sponsored by the pharmaceutical company, and a National Cancer Institute sponsored trial in Costa Rica (Costa Rica Vaccine Trial [CVT]). Complete results from the CVT trial have not been published; data on vaccine efficacy against persistent infection from less than three doses of the vaccine are now available in abstract and have been included in this review.

Study participants consisted of healthy females 15 to 25 years of age with six or less life-time sexual partners.[97, 100] Enrolment in the phase II trial was restricted to females with no history of Pap smear abnormality, cervical ablative treatment or active warts and who were seronegative for HPV types16/18 and HPV DNA negative by PCR for 14 high-risk HPV types. Eligibility criteria for the phase III PATRICIA trial were broader in that only women with a history of colposcopy were excluded. Phase III participants were enrolled regardless of baseline HPV status (by serology or PCR). Pregnant or breastfeeding women were also excluded from these trials.[97, 100]

Vaccine efficacy was examined from two perspectives: ITT and the according-to-protocol (ATP). The ITT analysis in phase II trials included women who were naive to all 14 high-risk HPV genotypes at month 0, received one or more doses of the vaccine, and for whom any outcome data were available.[97] The ITT analysis in the phase III PATRICIA trial included three study populations, all arising from the Total Vaccinated Cohort (TVC).

TVC included all women randomized into the study having received at least one dose of the vaccine and had any data available on efficacy endpoints. Outcome assessment or case counting began the day after first vaccination. This population represents the general population of women who may have abnormal baseline cytology or HPV infection at the time of vaccination.

- TVC-efficacy population (TVC-E) included the largest subset (99%) of TVC and includes participants who had normal or low-grade abnormal cytology at enrollment; outcome assessment began the day after first vaccination. Participants who were sero/PCR positive for type 16 or 18 at baseline were excluded from outcome assessment for that genotype
- TVC-naive population (TVC-N) included a subset (62%) of TVC who at study enrollment had normal cytology, were HPV DNA negative for all 14 oncogenic HPV genotypes, and seronegative for HPV types 16/18. Outcome assessment began the day after first vaccination. [100]

The ATP analysis approximates vaccine efficacy in individuals who receive a full series of HPV2 prior to being at risk of HPV exposure.

Outcome measures for HPV2 efficacy

Vaccine efficacy of HPV2 is reported for the following outcomes: incident infection, persistent infection, cytological abnormalities, cervical adenocarcinoma *in situ* (AIS), and a composite outcome labeled CIN2+ that includes, CIN2, CIN3, AIS and invasive carcinoma. Efficacy data against other gynecologic cancers are not available. These outcomes are available from 6.4 year follow-up of participants in phase II trial and three year follow-up of participants in the phase III PATRICIA trial.

Persistent infection is defined as two or more cervico-vaginal[97] or cervical (all trials) samples positive for the same HPV type at two consecutive assessments with no negative samples in between. Persistent infections lasting six to twelve months were assessed. CIN endpoints were assessed from histology specimens and independently confirmed by an external histopathology review panel blinded to vaccination history. Cytology and biopsy specimens were evaluated by PCR for HPV DNA. Biopsy lesions that were positive for multiple HPV genotypes were subjected to post-hoc 'type-assignment' analysis to identify the HPV type most likely associated with the observed adverse outcome. Underlying the premise of causality is that while incident HPV infections are common, a persistent infection is required for carcinogenesis to occur.[102] Causality was thus assigned to the HPV types that were also identified in at least one preceding cytology specimen. If preceding cytology specimens contained both the vaccine genotype (HPV type 16 or HPV type 18) and another HPV genotype, causality was ascribed to the vaccine genotype even though the duration of persistence may have been longer for non-vaccine HPV genotypes.[99]

HPV2 efficacy: Phase II trial results

Phase II ATP analysis reported HPV2 vaccine efficacy against six and 12 month-persistent HPV type 16/18-cervical infections of 96.0% (95% CI: 75.2-99.9) and 100.0% (95% CI: 52.2-100).[96] At 6.4 years of follow-up following receipt of HPV2, vaccine efficacy against HPV type 16/18-CIN2+ was 100% (95% CI: 51.3-100) resulting from zero cases in vaccinees and nine cases in controls.[103] (See table 5). Vaccine efficacy against all CIN2+ lesions independent of genotype was 71.9% (95% CI: 21-92).[103]

HPV2 efficacy: Phase III trial results

Final, event-driven analysis of phase III PATRICIA trial at 3 years of follow-up indicates ATP-vaccine efficacy of HPV2 against six and 12 month persistent HPV type 16/18 infection of 93.8% (95% CI: 91.0-95.9) and 91.2% (95% CI: 85.9-94.8) respectively[99] (See table 5). ATP-vaccine efficacy against HPV type16/18 CIN2+ was 92.9% (95% CI: 79.9-98.3). There were four cases of HPV type 16/18-CIN2+ identified in vaccinees and 56 cases among controls. ITT analysis of vaccine efficacy in the TVC-E population against HPV type 16/18-CIN2+ lesions was 94.5% (95% CI: 86.2-98.4). This resulted from five cases of CIN2+ associated with HPV types 16/18 among vaccinees compared to 91 cases among the control arm.

As several individuals had infections from multiple oncogenic HPV types, additional post-hoc analysis was conducted to evaluate causality using the HPV type-assignment algorithm. The vaccine efficacy in the TVC-E cohort for HPV types 16/18 following this exercise was 97.7%.

End-of-study analysis at up to 4 years of follow-up indicates ATP-vaccine efficacy of HPV2 against CIN2+ due to HPV types 16/18 of 94.9% (95% CI: 87.7-98.4).[104] After HPV type assignment, efficacy of HPV2 against CIN2+ due to HPV types 16/18 was 98.9% (95% CI: 93.8-100).[104]

Table 5: Efficacy of HPV2 (Cervarix™) against the combined incidence of vaccine-type-related infection of six and 12-month duration and cervical intraepithelial neoplasia in females 15 to 25 years of age.[98, 99]

I. Phase II trial, 6.4 year follow-up[98]								
	Vaccine (n=560)			Control (n=553)			Efficacy (%) (95% CI)	p value
Outcomes	n	Cases	Rate*	N	Cases	Rate*		
Total vaccine cohort – naïve (TVC-N)								
HPV type16/18 CIN2+	481	0	N/A	470	9	N/A	100 (51.3-100)	N/A
All CIN 2+	505	5	N/A	497	17	N/A	71.9 (20.6-91.9)	N/A
II. Phase III trial, mean follow-up, 34.9 months (n=18,644)[99]								
According to protocol (ATP)								
	Vaccine (n=8093)			Control (n=8069)			Efficacy (%) (95% CI)	p value
Outcomes	n	Cases	Rate*	n	Cases	Rate*		
6-month persistent infection HPV type 16/18	7177	32	N/A	7122	497	N/A	93.8 (91.0-95.9)	<0.0001
12-month persistent infection HPV type 16/18	7035	21	N/A	6984	233	N/A	91.2 (85.9-94.8)	<0.0001
HPV type 16/18 CIN2+	7344	4	0.02	7312	56	0.32	92.9 (79.9-98.3)	<0.0001
HPV type 16/18 CIN2+ after HPV type assignment	7344	1	0.01	7312	53	0.30	98.1 (88.4-100)	<0.0001
HPV type 16/18 CIN3+	7344	2	0.01	7312	10	0.06	80.0 (0.3-98.1)	0.0221
HPV type 16/18 CIN3+ after HPV type assignment	7344	0	0.00	7312	8	0.05	100 (36.4-100)	0.0038
Total vaccine cohort-efficacy (TVC-e)								
	Vaccine (n=8093)			Control (n=8069)			Efficacy (%) (95% CI)	p value
Outcomes	n	Cases	Rate*	n	Cases	Rate*		
HPV type 16/18 CIN2+	8040	5	0.02	8080	91	0.39	94.5 (86.2-98.4)	<0.0001
HPV type 16/18 CIN2+ after HPV type assignment	8040	2	0.01	8080	87	0.37	97.7 (91.0-99.8)	<0.0001
HPV type 16/18 CIN3+	8040	2	0.01	8080	22	0.09	90.9 (60.8-99.1)	<0.0001
HPV type 16/18 CIN3+ after HPV type assignment	8040	0	0.00	8080	20	0.09	100 (78.1-100)	<0.0001
Total vaccine cohort (TVC)								
	Vaccine (n=9319)			Control (n=9325)			Efficacy (%) (95% CI)	p value
Outcomes	n	Cases	Rate*	n	Cases	Rate*		
HPV type 16/18 CIN2+	8667	82	N/A	8682	174	N/A	52.8 (37.5-64.7)	<0.0001
HPV type 16/18 CIN3+	8667	43	N/A	8682	65	N/A	33.6 (-1.1-56.9)	0.0422

*Rate is expressed as number of cases per 100 person years.

HPV2 efficacy following less than three doses of the vaccine

In the Costa Rica Vaccine Trial, in which 7466 females 18-25 years of age were randomized to receive Cervarix™ or control vaccine, vaccine efficacy (VE) of <three doses against 1 year persistent infection for HPV type 16/18 was assessed. Females who received one, two or three doses of the study vaccine were 384, 802 and 5967 respectively. Women included were type 16/18 PCR-negative at enrolment and had any outcome data available. At 4.2 years of median follow-up time, VE for one dose was 100% (95% CI: 67-100), for two doses was 84% (95% CI: 50-96), and for three doses was 81% (95% CI: 71-88).[105]

HPV2 efficacy against oncogenic HPV genotypes not included in the vaccine

The phase III trial was analyzed to determine cross-protection from persistent infection and disease outcomes from oncogenic HPV genotypes other than types 16/18, although the trial was not powered for these outcomes. At the final analysis in the TVC-naive population, HPV2 vaccine efficacy against CIN2+ was 100% (96.1% CI: 82.2-100) for the two most common non-vaccine containing oncogenic types 31/45; 68.2% (96.1% CI: 40.5-84.1) for the five most common non-vaccine-containing oncogenic HPV types 31/33/45/52/58 and 66.1% (96.1% CI: 37.3-82.6) for the ten most common non-vaccine containing oncogenic HPV types 31/33/35/39/45/51/52/56/58/59.[106] At the final analysis (mean follow-up 34.9 months, SD 6.4 after the third dose) the overall vaccine efficacy of HPV2 irrespective of the HPV type in the lesion among the TCV-naïve population was 70.2% (96.1% CI: 54.7-80.9) against CIN 2+ and 87.0% (54.9-97.7) against CIN 3+.[99]

HPV2 efficacy against clearing prevalent infection or preventing its sequelae

Three doses of HPV2 were not effective in clearing HPV type 16/18 infections present before immunization. VE against HPV type 16/18 CIN2+ in women who were PCR positive at baseline, regardless of serostatus was 5.8% (95% CI: -34.3-33.9).[99] Similarly, in the CVT trial, VE for viral clearance was 2.6% (CI: –10.1-13.8) at six months and -7.0% (CI: –31.7-13.0) at 12 months of follow-up.[101] HPV2 was also ineffective at clearing infections from HPV type 16/18-related genotypes.[101]

Additional data has also become available on the efficacy of HPV2 in the prevention of new CIN2+ in women who have previously undergone therapy for HPV-related cervical abnormalities. In a secondary analysis of the PATRICIA study, vaccination with HPV2 in women previously treated for cervical disease was associated with a reduction in the incidence of new CIN2+ disease due to any HPV type of 88.2% (95% CI: 14.8-99.7).[107]

In summary, evidence from high quality randomized controlled trials show HPV2 is a highly effective prophylactic vaccine against persistent infection from HPV types 16/18 and its related outcomes of carcinoma *in situ* (CIN) 2/3 and adenocarcinoma *in situ* (AIS).

As indicated in the product monograph, Cervarix™ is not intended to be a therapeutic vaccine.

IV.3. Immunogenicity

Background

The immune correlates of protection against HPV infection/disease are unknown at this time. As each vaccine is discussed below, the antibody tests in the immunogenicity studies are described. Immunogenicity data from bridging studies conducted in adolescents and older women are also presented. In vaccine studies, once efficacy is established in one study population, efficacy studies are frequently not conducted in other similar populations (e.g.: females of a different age category). The underlying premise of immunogenicity bridging studies is that if the trial population attains similar antibody levels as the population in which efficacy is already established, efficacy results can be bridged or inferred to the new population. In addition, HPV efficacy studies are not done in younger age groups because it is considered unethical to conduct cervical exams in adolescents and younger children.

HPV quadrivalent vaccine (HPV4): Gardasil® immunogenicity

Females 16 to 26 years

Immunogenicity of HPV4 in this population was reviewed in detail in the 2007 NACI Statement. One month after the third dose, 99.5% of HPV4 vaccine recipients had seroconverted to all four HPV4 types with antibody titres 10 to 100 times higher than corresponding antibodies produced by natural infection.

Variation is seen between HPV antibody test results. Although about 40% of vaccine recipients were HPV type 18 seronegative at the end of the study visits in the phase III trials (mean 44-month follow-up) described above efficacy against HPV type 18-associated CIN and AIS continued at over 98% irrespective of antibody level.[108] The Competitive Luminex Immunoassay (cLIA) measures only one monoclonal neutralizing anti-HPV antibody and thus might under represent the total protective antibody levels.[109] To evaluate this possibility, a direct-binding IgG assay specific for the HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 VLP types was developed. Using this assay, immunization with HPV4 elicited high levels of VLP type-specific IgG that could be measured in 100% of individuals four years post-vaccination.[110] HPV4 has also demonstrated a robust anamnestic response to an antigen challenge at 60 months post vaccination with rapid rebound of antibody levels following the challenge,[111] to levels similar or higher than those seen shortly following the three dose series.[112]

Immunogenicity of HPV4 in females >24 years

Immunogenicity of HPV4 in females aged 24 to 45 years was assessed in a randomized, placebo-controlled clinical trial. At month 7, following three doses of HPV4 at day 1, month 2 and month 6, results were: anti-HPV type 6 seropositive 98% (n=1242); anti-HPV type 11 seropositive 98% (n=1238); anti-HPV type 16 seropositive 99% (n=1264) and anti-HPV type 18 seropositive 97% (n=1406).[85] Compared to females 16 to 23 years of age who participated in previous trials, antibody responses in older women enrolled in this study are comparable for HPV type 16 and slightly lower for HPV types 6, 11 and 18.

Immunogenicity of HPV4 in males

Immunogenicity of HPV4 (Gardasil®) in males 16 to 26 years of age (n=2025) was assessed in the male clinical trial (Protocol 020) [88] using a type-specific competitive Luminex immunoassay (cLIA).[113] Geometric mean titre and seroconversion results are summarized in Table 6; it should be noted that they are consistent only within each HPV type and cannot be compared across types. Seroconversion rates of 97-99 percent were seen at 7 months, and these persisted to 24 months for serotypes 6, 11 and 16 with a decline in the seroconversion rate noted for serotype 18.

Table 6: Immunogenicity of HPV4 vaccine (Gardasil®) among males 16 to 26 years (n=2025)[114]

	HPV4 (n=2025)			
Assay (cLIA v2.0)	**Geometric mean titre (GMT)**	**95% CI**	**Seroconversion rate**	**95% CI**
Anti-HPV type 6				
Day 1	<7	<7-<7	0.0	0-0.3
Month 7	446.0	422-474	98.9	98-99
Month 24	80.3	76-85	90.8	89-93
Anti-HPV type 11				
Day 1	<8	<8-<8	0.0	0-0.3
Month 7	624.2	594-656	99.2	98-100
Month 24	94.5	90-100	95.6	94-97
Anti-HPV type 16				
Day 1	<11	<11-<11	0.0	0-0.3
Month 7	2402.5	2271-2542	98.8	98-99
Month 24	347.8	329-367	99.3	99-100
Anti-HPV type 18				
Day 1	<10	<10-<10	0.0	0-0.3
Month 7	402.2	380-426	97.4	96-98
Month 24	38.7	36-41	62.3	59-65

In males 10 to 15 years of age (n=508; Protocol 016)[89] and 9 to 15 years of age (n=838; Protocol 018)[115] high rates of seroconversion were seen (Table 7).

Protocol 016 also establishes non-inferiority of immune response among young males and females compared to older females. In addition, combined analysis of male participants in all three trials (016, 018 and 020) demonstrates non-inferiority of immune response (immunobridging) of younger males (9-15 years of age) when compared to older males (16 to 26 years of age) in whom efficacy has been demonstrated.[90]

Table 7: Anti-HPV seroconversion* among males 9 to 15 years of age compared to males 16 to 26 years of age.[90]

Assay	9 to 15 year old males			16 to 26 year old males		
	N**	%	95% CI	N**	%	95% CI
HPV type 6	885	99.9	99.4-100	1093	99.8	98.1-99.4
HPV type 11	886	99.9	99.4-100	1093	99.2	98.4-99.6
HPV type 16	883	99.8	99.2-100	1136	98.8	97.9-99.3
HPV type 18	888	99.8	99.2-100	1175	97.4	96.3-98.2

* Seroconversion is defined as HPV type 6 cLIA (competitive Luminex immunoassay) ≥20 mMU (milliMerck units)/mL, HPV type 11 cLIA ≥16 mMu/mL, HPV type 16 cLIA ≥20 mMU/mL and HPV type 18 cLIA ≥24 mMU/mL at month 7

** N is defined as the number of subjects in the relevant per protocol immunogenicity population (9 to 15 year old males from protocol 016 and 018, and 16 to 26 years of age males from protocol 020).

Immunogenicity with alternate schedules of HPV4

Immunogenicity bridging studies reported on previously, such as the study by Block *et al.*, demonstrate higher neutralizing antibody response to HPV4 vaccine in adolescent compared to young adult females. A recent Canadian study by Dobson *et al*. [116] assessed whether antibody responses to HPV types 6, 11, 16 and 18 are non-inferior at seven months following the initiation of a two-dose pediatric/adolescent regimen compared to a three-dose adult regimen of HPV4 vaccine. Healthy females 9 to 13 years of age received either a two-dose (0, 6 months) or three-dose (0, 2 and 6 months) regimen and females 16 to 26 years of age (non-pregnant, <5 sexual partners, no history of genital warts or CIN and not previously vaccinated) received three doses (0, 2 and 6 months). Antibody responses among those receiving the two-dose regimen were non-inferior at month 7 for all four HPV types, as compared to three-dose regimens are seen below.

Table 8: Immunogenicity of quadrivalent HPV vaccine: Comparison of two versus three-dose regimens in females 9 to 13 years of age.

Assay (cLIA v2.0)	GMT ratios (95% CI)		
	Group 1 compared to Group 3*	Group 1 compared to Group 2*	Group 2 compared to Group 3*
Anti-HPV type 6	2.37 (1.78-3.14)	1.17 (0.88-1.56)	2.02 (1.52-2.67)
Anti-HPV type 11	1.86 (1.53-2.25)	1.11 (0.92-1.35)	1.67 (1.38-2.02)
Anti-HPV type 16	2.10 (1.62-2.73)	0.96 (0.74-1.24)	2.20 (1.69-2.85)
Anti-HPV type 18	1.84 (1.47-2.31)	0.70 (0.56-0.88)	2.62 (2.09-3.29)

*Group 1 (n=259): healthy girls 9 to 13 years of age, two doses of vaccine at 0, 6 months; Group 2 (n=261): healthy girls 9 to 13 years of age, three doses of vaccine at 0, 2 and 6 months; Group 3 (n=310): females 16 to 26 years of age, three doses of vaccine at 0, 2 and 6 months.

Ongoing evaluation is planned at months 18, 24 and 36, including T-cell and B memory cell assays and clinical evaluation for HPV infection and cervical dysplasia.

HPV bivalent vaccine (HPV2): Cervarix™ immunogenicity

Immune response to HPV2 in phase II and III trials was measured using an in-house type-specific binding enzyme-linked immunosorbent assay (ELISA) developed by the manufacturer. ELISA measures total IgG antibodies induced by the vaccine. The trials compare vaccine induced antibody response to the test's seropositive threshold, and to the antibody levels induced by natural infection.

Pseudovirion-based neutralization assay (PBNA) is a newer assay, developed by the National Cancer Institute in the US, and since then replicated in numerous laboratories including the GSK laboratories. This assay measures neutralizing antibodies (Nab) produced by the vaccine and thought to correlate with a functional protective effect of the HPV vaccine. This assay was used to compare the immune response induced by the bivalent and quadrivalent vaccine in a head-to-head trial [117] discussed later. The ELISA assay correlates well ($r \geq 0.89$ for both HPV type 16 and HPV type 18) with Nab measured by the company's in-house pseudovirion neutralization assay.[118]

A subset of participants in this head-to-head comparison trial between the two vaccines also had immune response analyzed by in-house assays (ELISA and cLIA) belonging to both manufacturers. Good correlation was found between these two assays ;[119] thus, the use of in-house vaccine-specific virus-like-particles does not appear to be biasing the measurement of the vaccine induced immune response.

Immunogenicity of HPV2 in females

Immunogenicity data for approximately 2200 females 15 to 25 years of age from a number of phase II and III protocols[97, 100, 120] at seven months and at 7.3 year follow-up (n=304 women)[121] are available. Over 99% of women seroconverted to both vaccine genotypes, and seven-month anti-HPV type 16 geometric mean titer (GMT) were 9341.5 EU/mL (95% CI: 8760-9961) with anti-HPV type 18 GMT of 4769.6 EU/mL (95% CI: 4491-5065).[99] Month seven antibody titres were 300-fold (HPV type 16) and 200-fold (HPV type 18) higher than those induced by natural infection.[99]

Immunogenicity bridging data for 9 year old, [122] 10 to 14 year old, [2, 123] and 26 to 55 year old females [124] are seen in Table 8. Vaccine induced antibody response was inversely correlated with age. The highest GMTs were noted in adolescents and these were more than twice the level measured in 15 to 25 years old females. All participants in all age groups were seropositive at seven months after three doses of HPV2.

Table 9: Anti-HPV type 16/18 GMTs (EU/mL) in females 9 to 55 years of age.

Assay (ELISA) Study cohorts	Anti-HPV type 16		Anti-HPV type 18	
	Geometric mean titre	95% CI	Geometric mean titre	95% CI
9 years				
Month 7 (122)	31252.5	25463.6-38357.4	12628.5	10142.6-15723.8
10 to 14 years				
Month 7 (123)	19882.0	18626.7-21221.9	8262.0	7725.0-8836.2
Month 18 (123)	3888.8	3605.0-4195.0	1539.0	1418.8-1670.3
Month 36 (125)	2675.5	2484.9-2880.8	972.0	896.5-1054.0
Month 48	2374.9	2205.7-2557.0	864.8	796.9-938.4
15 to 25 years				
Month 7 (99)	9341.5	8760.4-9961.1	4769.6	4491.2-5065.3
Month 24 (124)	1730.7	1462.3-2048.5	673.6	568.3-798.4
Month 36 (126)	1491.5	1260.9-1764.1	485.1	406.6-578.7
Month 83 (127)	383.4	N/A	251.0	N/A
26 to 45 years				
Month 7 (120)	4029.2	3402.7-4771.0	1837.3	1602.1-2107.0
Month 24 (127)	733.0	603.7-890.1	280.8	235.3-335.1
Month 36 (127)	607.2	502.8-733.3	220.1	184.5-262.5
46 to 55 years				
Month 7 (120)	2566.8	2181.2-3020.6	1313.0	1145.6-1504.9
Month 24	472.9	396.8-563.6	185.7	156.3-220.6
Month 36 (127)	363.9	301.6-439.1	136.9	114.9-163.0

N/A, confidence intervals were not reported

Durability of immune response to HPV2 in females

Approximately 300 females 15 to 25 years of age have been followed out to 8.4 years; [128] of these, 100% remain seropositive for both antibodies with levels 13-fold and 11-fold higher than that induced by natural infection to HPV type 16 and HPV type 18 respectively. Immune memory to HPV type 16 and HPV type 18 also remains strong seven years post initial series.[129] Antigen-specific CD4 T cell response for HPV type 16 and HPV type 18 was present in 89% and 63% of participants and memory B cell response to HPV type 16 and HPV type 18 was present in 74% and 78% of participants.

Among adolescents, following HPV2, 100% of participants remained seropositive to both anti-HPV types 16/18 at 4 years.[130] The associated GMTs were much higher than the plateau level noted for 15 to 25 year olds. Thirty-six month follow-up data are available for 26 to 45 and 46 to 55 years old females; 100% of women remained seropositive with antibody titres in the oldest age group reported to be ≥8-fold higher than those seen following natural infection.[124].

Immune responses following a booster dose of HPV2

A subset of phase II trial participants received a booster, or fourth dose, of HPV2 at approximately seven years after the initial vaccination series.[129] At one week post-vaccination, a significant and rapid boost to both HPV type 16 and HPV type 18 antibody levels was seen (Table 10). At one month after booster vaccination, HPV type 16/18 GMTs were 21 and 17-fold higher than pre-booster dose levels. Boosting of T and B cell immune responses was also noted. In addition, the fourth dose also boosted HPV type 31 and HPV type 45 antibody titres as measured by ELISA.[129]

Table 10: Anamnestic response to a booster dose of Cervarix™ in females seven years after the initial three-dose vaccination series.[129]

	Anti-HPV type 16	Anti-HPV type 18	Anti-HPV type 31	Anti-HPV type 45
GMT (EL.U/mL)				
Pre	720.7	502.9	209.4	192.9
Day 7	5894.9	3916.2	2228.2	2530.5
Month 1	15 410.7	8362.7	3630.8	4253.8
T-cells (% responders)*				
Pre	88.9	63.0	78.3	59.1
Month 1	100	96.9	95.2	95.2
B-cells (% responders)**				
Pre	74.1	77.8	45.8	45.8
Month1	100	100	95.8	95.8

* >500 specific CD4 T-cells expressing ≥ 2 of 4 immune markers

**>0 specific memory B-cells per million cells

Cervical immune response in females following three doses of HPV2

Secretory antibodies have been detected in the cervico-vaginal fluid up to 24 months after vaccine in cohorts 15 to 55 years of age;[127] the level of secretory antibodies correlated well with the antibody level in the serum.[131]

Male immune response to three doses of HPV2

In a phase I/II study of 270 Finnish males 10 to 18 years old in which HPV2 was administered at 0, 1 and 6 months, [132] 100% of study participants seroconverted after two doses. The third dose of the vaccine resulted in four-fold and two-fold increase in HPV type 16 and HPV type 18 antibody levels as compared to two doses.

Higher antibody responses to HPV2 have been observed in males compared to females. Peak GMTs in males 10 to 18 years old were 22 639.7 (95% CI: 19 825.5-25 853.4) for HPV type 16, and 8416.1 (95% CI: 7215.0-9817.1) for HPV type 18. In the subset of boys aged 10 to 14 years old, antibody levels were 27 891.6 (95% CI: 23 975.6-32 447.2) for HPV type 16 and 10 593.7 (95% CI: 8875.8-12 644.0) for HPV type 18. These responses were also higher than those reported among females 10 to 14 years of age[133] or males 15 to 18 years of age.[132]

Immune responses in females following HPV2 administered at 0, 1, 12 months

Immune responses to HPV2 (seroconversion rate and GMTs for both HPV type 16 and HPV type 18) administered with the standard 0, 1, 6 schedule compared to the 0, 1, 12 schedule were non-inferior in a randomized controlled trial in 804 healthy young women 15 to 25 years of age in Italy, Romania and Slovakia.[134]

Immune responses in females following two doses of HPV2

In an age-stratified, randomized controlled trial comparing the standard three-dose regimen of HPV2 to a two-dose schedule at 0 and 6 months in healthy females 9 to 25 years of age, all subjects in both arms were seropositive at month 7 and month 24.[98,135] GMTs are seen Table 11. The three-dose schedule was non-inferior to a two-dose schedule in this age group. A subset of participants 9 to 14 years of age who received a two-dose schedule also had a non-inferior response compared to females 15 to 25 years of age up to month 24.[135]

Table 11: Anti-HPV type 16/18 GMTs (EU/mL) in females 9 to 25 years of age following two or three doses of Cervarix™.[98,135]

Assay (ELISA)	Anti-HPV type 16		Anti-HPV type 18	
Study cohorts	**GMT**	**95% CI**	**GMT**	**95% CI**
9 to 25 years two-dose Month 7	8093	7275-9002	4639	4154-5180
9 to 25 years three-dose Month 7	13165	11834-14645	5089	4567-5671
9 to 25 years two-dose Month 24	1326	1168-1506	684	591-791
9 to 25 years three-dose Month 24	2390	2007-2847	852	721-1007

Comparison of immunogenicity of three doses of the HPV4 (Gardasil®) and HPV2 (Cervarix™)

Einstein and colleagues conducted a head to head comparison of the two vaccines in a randomized controlled trial involving 1106 women stratified in three age groups, 18 to 26, 27 to 35 and 36 to 45 years.[117, 136] This is a longitudinal study with planned immune response follow-up to 60 months. At seven months, HPV2 recipients across all age groups had GMTs that were several fold higher for both HPV type 16 and HPV type 18 Nab (Table 12). CVS antibody positivity rates were also higher in the HPV2 recipients at 7 months. While HPV type 16 specific memory B cell response was similar in both vaccine arms, HPV type 18 response was higher in HPV2 recipients at 7 months but was no longer higher at month 36.[137] A subset of recipients also had month 7 antibody titres assessed by both GSK's ELISA and Merck's cLIA assay. HPV2 recipients had higher antibody titres for anti-HPV type 16 and anti-HPV type 18 by both assays.[119] Differences in humoral and cellular immune responses between the two vaccines persisted over a 24-month follow-up period (Table 12).

Table 12: Immune response to bivalent and quadrivalent HPV vaccines in females 18 to 45 years of age .[117, 136]

	HPV2 (Cervarix™)		HPV4 (Gardasil®)	
	Anti-HPV type 16	**Anti-HPV type 18**	**Anti-HPV type 16**	**Anti-HPV type 18**
Serum N GMT* ratio (ratio of type specific response for Cervarix™/Gardasil®)				
Month 7	2.3-4.8x higher†	6.8-9.1x higher†		
Month 18	2.4-5.1x higher†	7.9-9.8x higher†		
Month 24	2.4-5.8x higher†	7.7-9.4x higher†		
Serum T-cells (% responders)**				
Month 7	N/A	N/A	N/A	N/A
Month 18	92.5†	78.6†	40.0	42.4
Month 24	90.9†	74.3†	60.0	40.0
Serum B-cells (% responders)***				
Month 7	89.8	88.7†	94.3	66.1
Month 18	86.7†	74.5†	58.6	45.2
Month 24	83.3	76.3†	66.7	52.9
CVS nAb*				
Month 7	81.3†	33.3†	50.9	8.8
Month 18	20.9	7.0	14.9	0.0
Month 24	24.4	2.2	11.6	0.0

* measured by PBNA

** >500 specific CD4 T-cells expressing ≥2 of 4 immune markers; assay done on a subset of participants.

*** >0 specific memory B-cells per million cells; assay done on a subset of participants.

† Result is statistically significant.

IV.4. Vaccine Administration and Schedule

Both HPV vaccines are administered intramuscularly as three separate 0.5 mL doses, using slightly different schedules.

- Cervarix™ should be injected in the deltoid muscle using a 0, 1 and 6 month schedule. The second dose can be given up to 2.5 months after the first dose and the third dose can be given between 5 and 12 months after the second dose.
- Gardasil® should be administered in the deltoid muscle, or the anterolateral upper thigh, using a 0, 2 and 6 month schedule. The minimum interval between the first and second dose is one month and the second and third doses should be separated by an interval of at least 12 weeks.[1]
- The schedule and dosage of Gardasil® for males is the same as for females.

Interrupted vaccine schedules

If either vaccine schedule is interrupted, the vaccine series does not need to be restarted. If the series is interrupted after the first dose, the second dose should be given as soon as possible. If only the third dose is delayed, it should be administered as soon as possible.

Booster doses and re-immunization

At this time, booster doses are not indicated for either HPV vaccine.

IV.5. Pre- or post-immunization testing

Neither pre nor post-vaccination testing is recommended. Testing methods are not routinely available.

IV.6. Storage requirements

Both HPV2 and HPV4 vaccines should be stored between +2°C and +8°C. The vaccines should be discarded if frozen.

IV.7. Simultaneous administration with other vaccines

Studies have demonstrated non-inferiority with respect to safety and immunogenicity when HPV4 (Gardasil®) vaccine is administered with either hepatitis B (Recombivax HB®, Merck Research Laboratories) or DTaP-IPV vaccine (Repevax®, Sanofi Pasteur).[138, 139] Similarly, immune responses after concomitant administration of Gardasil®, conjugate meningococcal vaccine (Menactra®, Sanofi Pasteur) and other adult/adolescent formulations of tetanus, diphtheria and acellular pertussis vaccines (Tdap) (Adacel®, Sanofi Pasteur) have been shown to be non-inferior to nonconcomitant administration.[140]

Five co-administration studies of HPV2 (Cervarix™) with other adolescent vaccines have been conducted to date (GSK111567, GSK110886, GSK 108464, GSK107682 [120, 141]. These studies demonstrate non-inferiority with respect to safety and immunogenicity when HPV2 vaccine is administered with either hepatitis B (Engerix™, GSK) (GSK110886), hepatitis A/B vaccine (Twinrix™), Tdap (Boostrix™), Tdap-IPV (Boostrix™-Polio), or quadrivalent meningococcal conjugate vaccine, MCV4 (Menactra™).

HPV4 and HPV2 are not live vaccines and have no components that have been found to adversely affect the safety or efficacy of other vaccines. 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. Administering all indicated vaccines together at a single visit increases the likelihood that adolescents and young adults will receive each of the vaccines on schedule. Each vaccine should be administered using a separate syringe at a different anatomic site.

IV.8. Adverse events

HPV quadrivalent vaccine (HPV4): Gardasil® adverse events

Slade *et al.* [142] report on 2.5 years of post-licensure safety surveillance data to VAERS (Vaccine Adverse Event Reporting System) in the US. VAERS shares the limitations inherent to many passive surveillance systems. Its data should be interpreted with caution, because not all events are reported, and not all reported events are systematically validated, and many may have only coincidentally followed immunization.

Adverse events (AEs) following receipt of HPV4 reported to VAERS have been consistent with pre-licensure data. AEs following receipt of HPV4 have been reported at a rate of 53.9 per 100 000 doses (total of 12 424 reports) between June 2006 and December 2008. Reported rates per 100 000 doses distributed were 8.2 for syncope, 7.5 for local site reactions, 6.8 for dizziness, 5.0 for nausea, 4.1 for headache, 3.1 for hypersensitivity reactions, 2.6 for urticaria,

and ≤0.2 for venous thromboembolic events, autoimmune disorders, Guillain-Barré syndrome, anaphylaxis, death, transverse myelitis, pancreatitis and motor neuron disease. A total of 772 reports (6.2%) were described as serious adverse events, including 32 deaths. Expert review of serious adverse events and deaths following receipt of HPV4 have not found a common medical pattern or clustering of events to suggest that they were caused by the vaccine, and proportional reporting ratios for deaths do not suggest a causal association.[142]

Agorastos *et al.* reviewed the 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 adverse events following immunization (AEFI) reported in all jurisdictions being local injections site reactions. No pattern of serious AEFI suggesting a causal relationship to vaccination was observed.[143]

An Australian report indicates an anaphylaxis rate of 2.6 per 100 000 doses of HPV vaccine, using the stringent Brighton criteria.[144] While this rate is higher than the rates reported for other vaccines, it is still less common than the WHO categorization of adverse events which are "very rare" (1 in 10 000). Gardasil® product information has been updated, advising healthcare practitioners to be prepared for the possible occurrence of anaphylaxis following HPV4 vaccination.

Updated safety analysis of HPV4 [145] has recently been published. It combines clinical trial data (3.6 years mean follow-up time) from five clinical trials and includes 21 480 females (9 to 26 years of age) and males (9 to 16 years of age) who received at least one dose of vaccine or placebo. In this study most injection-site adverse events were mild-moderate in intensity (78%). The most commonly reported injection-site adverse events among vaccine recipients were pain (81.3%), swelling (24.2%) and erythema (23.6%). Overall, the proportion of injection-site adverse events was significantly higher among vaccine recipients compared to both aluminum-containing (83% versus 77%, $p<0.05$) and non-aluminum containing (83% versus 49%, $p<0.05$) placebos. Systemic adverse events were comparable between the vaccine and placebo groups: headache (26% versus 28%), pyrexia (13% versus 11%) and nausea (6% versus 6%). Eight subjects experienced a treatment-related adverse event including six in the vaccine group and two in the placebo group. Among 18 deaths, all were unrelated to the study treatment.

In the trial of older females (24 to 45 years of age) by Munoz *et al.*, vaccine-related adverse events were reported but not subject to statistical comparison.[85] Among study participants, the proportion reporting one or more adverse event following receipt of HPV4 was 86.9% (76.8% injection-site, 59.2% systemic) compared with 81.2% following placebo (64.3% injection-site, 60.0% systemic). Serious adverse events were reported at 0.2% (n=3) following vaccine and 0.4% (n=7) following placebo.[85]

Combined safety data from male clinical trials of HPV4 (016, 018 and 020) [90] show an adverse event prevalence following vaccination of 74% (64% injection site, 18% vaccine-related systemic), compared with 64% of placebo recipients (53% injection site, 15% vaccine-related systemic). Among those with injection site AEs (64%), pain (62%), erythema (17%) and swelling (14%) were most common. Among systemic AEs (18%), headache (12%) and pyrexia (8%) were most frequently reported. Serious adverse events occurred in 0.3% (n=9) of vaccine recipients compared with 0.0% (n=1) of placebo recipients. None of these events were determined to be vaccine-related. No deaths were reported.

Table 13: Summary of adverse events reported among males 9 to 26 years of age (Days 1 to 15 following any dose of HPV4 Protocols 016, 018 and 020 [90]).

Subjects	Gardasil® (N=3002)		Placebo** (N=2219)	
	n	%	n	%
With one or more AE	2216	74	1417	64
Injection-site AEs*	1927	64	1177	53
Systemic AEs	1118	37	723	33
Vaccine-related systemic AEs	527	18	338	15
With serious AEs	9	0.3	1	0
Vaccine-related serious AEs	0	0	0	0
Deaths	0	0	0	0
Discontinued due to AE	6	0.2	4	0.2
Discontinued due to a vaccine-related AE	4	0.1	3	0.1

* All injection site adverse events are considered vaccine-related

N=number of subjects with follow-up; n=number of subjects in each category

** AAHS (amorphous aluminum hydroxyphosphate sulfate) placebo used for protocol 020 (males 16 to 26 years); saline placebo used for protocols 016 and 018 (males 9 to 15 years)

In addition to combined clinical trial data (above), pre-licensure trial results assessing younger males (9 to 15 years of age, protocols 016 and 018) are published. Block *et al.* report on adverse events following receipt of HPV4 in a non-inferiority immunogenicity study of males and females ages 10 to 15 years compared with females ages 16 to 23 years.[89] Among males who received at least one dose of the vaccine, 79.2% experienced an adverse event following immunization (74.0% injection site, 27.2% systemic). The proportion reporting at least one injection-site or systemic adverse event was significantly lower among boys (71.4%) and girls (79.4%) compared to older females (86.3%) ($p<0.001$, $p=0.004$ respectively). Whereas significantly more boys (13.8%) and girls (12.8%) ages 10 to 15 years compared to females ages 16- to 23 years (7.3%) reported fevers ≥37.8°C within five days of vaccination ($p<0.001$, $p=0.004$ respectively). The prevalence of serious adverse events among males was 0.2% (n=1), and these adverse events were determined to be unrelated to the vaccine.

HPV bivalent vaccine (HPV2): Cervarix™ adverse events

Petaja *et al.* evaluated the immunogenicity and safety of the HPV2 vaccine in healthy males 10 to 18 years of age.[132] Local adverse events (pain, redness and swelling at injection site) and systemic adverse events (myalgia) were more commonly reported in HPV2 recipients than in the HBV vaccine control group. These AEs were mild in nature and vaccine compliance was high (97%) in both the vaccine and control arms.[132]

Results of three pooled studies to examine adverse events related to Cervarix™ or AS04 adjuvanted vaccine are now available.[80, 146, 147] These studies were designed to evaluate risk of serious adverse events (SAE)[146], medically significant conditions (MSC)[146], new onset chronic disease (NOCD),[146] new onset autoimmune disease (NOAD)[80, 146], and adverse pregnancy outcomes.[146, 147]

Table 14 provides incidence of adverse events in Cervarix™ recipients >9 years of age. Cervarix™ administration resulted in a higher rate of solicited local (pain, redness, and swelling) and systemic reactions (fatigue, arthralgia and myalgia) within seven days of vaccine administration. The majority of local reactions were mild to moderate in intensity. The rates of severe local reactions were low among all age groups. There was no increase in adverse events with successive vaccine doses (PI, USA).

Table 14: Incidence (%) of injection site and systemic adverse events in female HPV2 (Cervarix™) trial participants.

	9 years[120]		10 to 14 years[146]		15 to 25 years[146]			>25 years[146]	
	HPV2	HAB	HPV2	HAV360	HPV2	HAV720	Al(OH)3	HPV2	Al(OH)3
Local reactions									
No. of doses	256	267	3528	3059	15 020	8747	1567	4258	2918
Pain	74.2*	52.1	71.9*	41.3	82.8*	58.9	72.9	66.2*	41.5
Redness	43.4*	15.0	28.8*	13.7	31.4*	16.0	12.8	23.9*	9.5
Swelling	36.7*	12.4	24.8*	8.6	27.2*	10.1	10.8	21.7*	6.8
Systemic reactions									
No. of doses	256	267	3529	3058	15 015	8748	1565	4258	2916
Fatigue	23.4	22.1	29.2*	24.6	37.0*	35.3	31.7	22.6*	18.0
Fever	4.3	1.9	7.3	6.8	4.8	4.6	5.5	4.5	5.1
Gastrointestinal	6.3	10.1	12.4	11.3	14.3	14.0	15.9	8.4	9.4
Headache	19.5	16.9	28.8	25.4	31.9	30.8	36.5	21.6	20.2
Rash	2.3	2.6	4.6*	2.6	4.1	3.6	4.2	2.3	1.9
Arthralgia	4.7	6.7	11.7*	9.3	10.1*	8.6	-	9.3	7.6
Myalgia	17.6	11.2	29.2*	17.1	31.5*	26.5	-	16.7*	9.9
Urticaria	1.6	2.2	2.5	2.1	3.6	3.7	-	2.1	2.6

HAB=combined hepatitis A and B vaccine, HAV=hepatitis A vaccine (720 or 360 EU), $Al(OH)_3$=Aluminum hydroxide

New medical conditions: MSC, NOCD, NOAD, SAEs

Table 15 presents the rates of these outcomes from the pooled data bases; there are no differences in the development of these adverse events (MSC, NOAD, NOCD, SAE, and deaths) between HPV2 and control vaccine recipient.

Table 15: Age-stratified incidence of MSCs, NOCDs, NOADs, and SAEs in Cervarix™ and control [($Al(OH)_3$ or hepatitis A vaccine (720 or 360 EU)] vaccine recipients.[146]

	10 to 14 years		15 to 25 years			>25 years	
	HPV2	HAV360	HPV2	HAV720	$Al(OH)_3$	HPV2	$Al(OH)_3$
No of women	1194	1032	11 508	9315	553	1449	984
MSC	21.3	24.8	20.0	21.8	-	13.4	14.6
NOCD	3.3	3.0	1.7	1.7	1.1	1.0	1.0
NOAD	0.3	0.6	0.4	0.3	0.7	0.2	0.2
SAEs	2.3	2.4	3.4	3.5	8.4	1.1	0.9

HAV=hepatitis A vaccine (720 or 360 EU), $Al(OH)_3$=Aluminum hydroxide

As Cervarix™ employs a new adjuvant, one pooled study extensively examined the risk of developing autoimmune disease.[80] The analysis examined recipients of Cervarix™ (n=39 160) or AS04 containing vaccines (n=68 512). The length of follow-up for vaccinees varied with trial protocol. The overall risk of development of autoimmune disease in participants receiving AS04 containing vaccines or controls was 0.5%. The relative risk of developing a new autoimmune disease following Cervarix™ was 0.92 (95% CI: 0.7-1.22) and following any AS04 containing vaccine was 0.98 (95% CI: 0.80-1.21). Five deaths (one in vaccinee and four in the control groups) were reported in the pooled safety analysis; causes of deaths were motor vehicle accidents (2), bone sarcoma (1), diabetic ketoacidosis (1) and drowning (1). None were related to the study.

Comparison of adverse events of three doses of the HPV4 (Gardasil®) and HPV2 (Cervarix™)

Analysis by Einstein *et al.* compared the proportion of women reporting at least one unsolicited symptom within 30 days after any HPV vaccine dose.[117] Of the 553 women who received Cervarix™, 42.5% (95% CI: 38.3-46.7) reported adverse events, compared to 36.5% (95% CI: 32.5-40.7) of the 553 women in the Gardasil® group. Rates of medically significant conditions (MSCs) were 29.7% (95% CI: 25.9-33.7) and 26.8% (95% CI: 23.1-30.7) in the Cervarix™ and Gardasil® groups, respectively. Fatigue and myalgia were more frequently reported by women in the Cervarix group.[117]

Serious adverse events (SAE)

SAEs were reported by six women in the Cervarix™ group and seven women in the Gardasil® group, two of which were considered possibly related to vaccination (one grand mal convulsion which occurred one day after administration of the third dose of Cervarix™ and one spontaneous abortion which occurred 47 days after the first dose of Gardasil®). It is important to reiterate that decisions relating AEs to vaccination were based on the judgment of the investigator at the study site reporting the event. Withdrawals due to AEs were infrequent (five women in the Cervarix™ group and four women in the Gardasil® group).

Vaccination during pregnancy

HPV vaccines are not recommended for use in pregnancy. While neither vaccine has been causally associated with adverse outcomes of pregnancy or adverse events to the developing fetus, the data on vaccination in pregnancy are limited.

A recent study by Garland *et al*. [148] of pregnancies occurring among subjects during phase III clinical trials finds that administration of HPV4 did not demonstrate adverse pregnancy outcomes. In addition, a study of pregnancy outcomes from the Gardasil® pregnancy registry, based on voluntary post-marketing reports, showed rates of adverse outcomes such as spontaneous abortion and major birth defects that were not greater than the unexposed population rates.[149]

While Cervarix™ should not be administered to pregnant women or to women intending on becoming pregnant within two months of vaccination, data indicate the safety of this vaccine in pregnant women. Genotoxicity and reproductive toxicity of MPL, a component of the HPV2 adjuvant, has been assessed via *in vitro* assays and animal studies.[150] No abnormal effects have been demonstrated.

Epidemiologic studies have also examined pregnancy outcomes among Cervarix™ trial participants.[146, 147] Table 16 presents data on 1737 pregnancies among women and girls who received at least one dose of the HPV2 vaccine or one of three controls [($Al(OH)_3$ or hepatitis A vaccine (720 or 360 EU)] reported in 11 trials.[146] Overall there was no difference in pregnancy outcomes between the HPV vaccine and control arms (HAV360, HAV720, and $Al(OH)_3$).

Table 16: Pregnancy outcomes (adapted from Descamps[146]).

	10 to 14 years		15 to 25 years			>25 years		
	HPV2	HAV360	HPV2	HAV720	$Al(OH)_3$	HPV2	HAV720	$Al(OH)_3$
All pregnancies								
No of pregnancies	9	9	833	683	152	28	3	20
Spontaneous abortions (%)	-	-	9.5	7.6	11.8	7.1	-	20.0
Pregnancies with last menstrual period 30 days before to 45 days after a vaccine dose								
No of pregnancies	1	1	200	173	12	9	2	17
Normal infant/ pregnancy ongoing	100	-	64.0	69.4	83.3	77.8	100	52.9
Premature infant	-	100	3.5	2.3	8.3	-	-	-
Spontaneous abortion	-	-	11.0	5.8	8.3	11.1	-	17.6

HAV=hepatitis A vaccine (720 or 360 EU), $Al(OH)_3$ =Aluminum hydroxide

A pooled analysis from two phase III studies (PATRICIA and CVT) analyzed the rate of miscarriage from 3599 pregnancies reported in 26 130 women 15 to 25 years of age.[147] The miscarriage rate in HPV2 vaccine recipients and control vaccine recipients was 11.5% and 10.2%. A sub-analysis of pregnancies that began within three months of vaccination revealed a miscarriage rate of 14.7% and 9.1% in the HPV vaccine recipients and control arms respectively. These differences in rates were not statistically significant. Overall, there is no association between vaccination with Cervarix™ and rate of miscarriage.

Until additional information is available, initiation of the vaccine series should be delayed until after completion of the pregnancy. If a woman is found to be pregnant after initiating the vaccination series, completion of the three-dose regimen should be delayed until after pregnancy. If a vaccine dose has been administered during pregnancy, there is no indication for any intervention.

Vaccination during breastfeeding

Data on consequences of HPV vaccination of breastfeeding women on their infants are not available.

IV.9. Contraindications/precautions

Neither Gardasil®, nor Cervarix™, should be administered to individuals with a known history of hypersensitivity to any of the vaccine components. Bivalent HPV vaccine in prefilled syringes is contraindicated for persons with anaphylactic latex allergy.

IV.10. Other considerations

Vaccine Administration

In general, syncope can occur after any vaccination, most commonly among adolescents and young adults. To avoid serious injury related to a syncopal episode, HPV vaccine recipients should be observed for 15 minutes after vaccine administration.

Cervical cancer screening in women who have received HPV vaccine

While HPV vaccines have been shown to be highly effective against cancer precursors caused by HPV type 16 and HPV type 18, these two HPV types are responsible for approximately 70% of cervical cancer. Those vaccinated will still be susceptible to infection from other high-risk HPV

genotypes and women who were sexually active prior to receiving HPV vaccine may already have been infected with HPV type 16 or HPV type 18. All women should continue to take part in the currently recommended cervical cancer screening programs. As more females receive the vaccine, screening programs may be modified in either type and/or frequency of screening. This is an area requiring continued research and surveillance before guidelines can change.

Interchangeability of vaccines

Whenever possible, one brand of vaccine should be used to complete a vaccine series. If the brand of the previously received doses is not known, either vaccine may be used to complete series. Both vaccines provide protection against HPV types 16/18 and therefore patients are likely to achieve protective antibody levels against these HPV types. If less than three doses of HPV4 are administered, protection against HPV types 6/11 cannot be assured.

V. Recommendations

Background

Health Canada has authorized use of HPV4 and HPV2 vaccines in specific female populations:

- HPV4 (Gardasil®) is authorized for use in females 9 to 45 years of age for the prevention of infection caused by HPV types 6, 11, 16 and 18 and related diseases including cervical, vulvar and vaginal cancers and their precursors, cervical adenocarcinoma *in situ* (AIS) and genital warts (condyloma acuminata).
- HPV4 (Gardasil®) is also authorized for use in males 9 to 26 years of age for the prevention of infection caused by HPV Types 6, 11, 16, and 18 and for anogenital warts (AGW).
- HPV4 (Gardasil®) is also indicated in females and males 9 through 26 years of age for the prevention of anal cancer caused by HPV types 16 and 18 and anal intraepithelial neoplasia (AIN) grades 1, 2, and 3 caused by HPV types 6, 11,16, and 18
- HPV2 (Cervarix™) is authorized for use in females aged 10 to 25 years for the prevention of CIN 1, 2, 3 and cervical AIS due to HPV types 16/18.

The choice of vaccine for individuals and public health programs depends upon the importance of protection from external genital warts (EGW). If wart protection is desired, vaccination with HPV4 should be used. If the goal of vaccination is prevention of HPV type 16/18-related cancers, their precursors and AIS, either vaccine may be used.

As with any vaccine recommendations, it should be noted that provinces and territories should consider additional criteria such as economic, local programmatic / operational, and societal factors when considering inclusion of the following recommendations in publicly-funded immunization programs.

1. HPV vaccine (Cervarix™ or Gardasil®) is recommended for females between 9 and 13 years of age (NACI Recommendation Grade A).

This is the age before the onset of sexual activity for most females and the potential benefit would be greatest. While efficacy of the vaccine in this age group has not been demonstrated, immunogenicity bridging evidence implies that efficacy would be high.

2. HPV vaccine (Cervarix™ or Gardasil®) is recommended for females between 14 and 26 years of age (NACI Recommendation Grade A).

The efficacy of Cervarix™ and Gardasil® in preventing AIS and CIN2+ in this age group has been demonstrated. Prevention of external genital lesions has also been demonstrated in this group with HPV4. Females would benefit from Cervarix™ or Gardasil® even if they are sexually active 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. It is therefore recommended that females in this age group receive HPV vaccine.

3. HPV vaccine (Cervarix™ or Gardasil®) is recommended for females between 14 and 26 years of age who have had previous Pap abnormalities, including cervical cancer and EGW (NACI Recommendation Grade B).

Although these women may not have had infection from HPV types contained in the vaccine, they would still benefit from receiving HPV vaccine for the types to which they have not been exposed. They should be advised that the vaccine does not have any therapeutic effect on pre-existing HPV infections or cervical disease.

4. HPV vaccine (HPV2 or HPV4) may be administered to females over 26 years of age (NACI Recommendation Grade A (Gardasil®) Grade B (Cervarix™)).

NACI has determined that there is good evidence to recommend the use of Gardasil® in females between 27 and 45 years of age. Gardasil® has been shown to be immunogenic and safe in females between 24 and 45 years of age. Efficacy has been demonstrated in the same group among those *not* infected with the relevant HPV types at the time of vaccination. Efficacy of Cervarix™ has not been demonstrated in this age group, but immunogenicity bridging data suggest that the vaccine efficacy would be high in HPV type 16/18-naive women.

Using a composite end-point (cervical disease/external genital disease/type-specific infection that persisted for 6 months) to allow for more rapid assessment of HPV4 efficacy, immuno-bridging links vaccine efficacy against the composite end-point to five-year protection against CIN2 or 3 reported in trials in females between 16 to 23 years of age, implying similar protection against CIN2 or 3 among older females (24 to 45 years of age) compared to younger women (16 to 23 years of age).

Females between 24 and 45 years of age who are likely already sexually active and who may or may not have had previous Pap abnormalities, including cervical cancer, or have had genital warts or known HPV infection would still benefit from HPV4. These women may not have had infection with the HPV types included in the vaccine and are unlikely to have been infected with all four HPV types contained therein. In the clinical trial population studied, 67% of women enrolled were naïve via PCR and serology to all four HPV vaccine-types (6, 11, 16 and 18) and 90% were susceptible to three or four vaccine-types. While Canadian seroprevalence data are not available, clinical trial estimates are similar to a recent Australian population-based seroprevalence study in which the proportion of women between 30 and 49 years of age susceptible to HPV types 16 and 18 was between 61.3% and 70.0%.

Epidemiologic studies have shown that while peak risk for HPV infection is within the first five to 10 years of the first sexual experience, a second peak in HPV DNA prevalence is observed in women ≥45 years of age. Although the second peak is reduced compared to peak rates in younger women, this risk is not insignificant. While the reason for this second peak is not yet fully understood, receipt of HPV vaccine by previously unimmunized adult females could reduce the risk of HPV infection occurring later in life.

As these women may be infected with an HPV type contained in the vaccine and there is no readily available screening method to determine this, women should be made aware of the possibility that they are already infected with an HPV vaccine-type. Women should be informed that there are no data to suggest that the vaccine will have any therapeutic effect on pre-existing HPV type 16/18 infections and cervical disease.

As for all women who receive HPV vaccination, women in this age group should be informed that they must continue to participate in the cervical cancer screening program.

5. HPV vaccine (HPV2 or HPV4) is not recommended in females <9 years of age (NACI Recommendation Grade I).

No immunogenicity or efficacy data are available for females <9 years of age.

6. HPV4 (Gardasil®) is recommended in males between 9 and 26 years of age for the prevention of anal intraepithelial neoplasia (AIN) grades 1, 2, and 3, anal cancer, and anogenital warts (NACI Recommendation Grade A).

NACI has determined that there is good (Grade A) evidence to recommend the use of Gardasil® in males between 9 to 26 years of age. Gardasil® has been shown to be as immunogenic and safe in young male adolescents as it is in young female adolescents.[89, 115] Clinical trials demonstrate that Gardasil® decreases the incidence of

infection, AIN, anal cancer, and external genital lesions in young males aged 16 to 26 years.[88][92] As in females 9 to 13 years of age, immunogenicity bridging data implies that efficacy of Gardasil® among males of the same age would be high.[89] As with females, receipt of Gardasil® between 9 and 13 years of age prior to onset of sexual activity is recommended to maximize efficacy of the vaccine.

Males between the ages of 14 and 26 years would also benefit from Gardasil® even if they are already sexually active as they may not yet have HPV infection and are very unlikely to have been infected with all four HPV types in the vaccine. However, males who are already sexually active may be infected with one or more HPV types contained in the vaccine, and there is no readily available screening method to determine this. Therefore, these men should be made aware of the possibility that they are already infected.

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 AGWs in Canada is considerable, particularly among men whose incidence rates and incidence rate ratios compared to females have been increasing in recent years.[29, 30]
- 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 (OR=0.37; 95% CI: 0.083-1.6) although confirmation using a larger sample will be required due to inadequate precision around the estimate.[95]
- 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, ;[70-72, 74, 75, 148] this is based on assumptions that such transmission from males to females will be reduced, rather than observational data.[69]
- 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.[70, 151]

Furthermore, if herd immunity effects are significant, this may improve the impact of the program on health equity which is a significant factor in cervical cancer epidemiology.

The incremental cost of implementing an HPV program that includes males may be considerable. Estimated cost-effectiveness ratios have been shown to increase between 5 and 20-fold per quality-adjusted life year (QALY) for a male and female program compared with a female-only program. A recent cost-effectiveness analysis by Kim & Goldie estimates that inclusion of preadolescent boys into a routine program in the United States has cost-effectiveness ratios exceeding $100 000 per QALY using a range of disease, vaccine and screening assumptions.[152] Provinces and Territories may consider undertaking cost-effectiveness analyses using parameters specific to the Canadian / jurisdictional context to more precisely assess incremental costs.

7. HPV4 (Gardasil®) 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.

While Gardasil® is not currently indicated for prevention of penile, perineal, or perianal intraepithelial neoplasia, early clinical trial results show good efficacy (85.6%) against 6-month persistent infection, an important predictor for disease development.[153] While the total burden of HPV-associated cancers among males is estimated at 5.2% of all cancers worldwide.[38] increasing rates of anal cancer among males have been observed, paired with lower survival compared to females.[43, 44]

8. HPV4 (Gardasil®) is recommended in males who have sex with males (MSM) ≥9 years of age (NACI Recommendation Grade A).

NACI has determined that there is good evidence to recommend the use of Gardasil® in MSM. Compared to the general population, MSM have disproportionately high burden of HPV infection, particularly vaccine-preventable high-risk types 16 and 18.[52] Infection with high-risk HPV types in particular increases the risk of anal intraepithelial neoplasia (AIN) and is associated with cancer of the anus, particularly among MSM who are HIV-positive. Early receipt of Gardasil® would confer maximum benefit, particularly since MSM may become infected with HPV more rapidly due to the high rate of infection in the population.

MSM may still benefit from Gardasil®, even if they are already sexually active, as they may not yet have HPV infection and are unlikely to have been infected with all four HPV types in the vaccine. However, there is no readily available screening method to determine whether those who are sexually active have already been infected with a HPV type contained in the vaccine. Therefore, these men should be made aware of the possibility that they are already infected.

9. Cervarix™ is not recommended in males at this time (NACI Recommendation Grade I).

While there are data on immunogenicity and safety of Cervarix™ in adolescent males, data on efficacy against infection and disease end points in males are lacking at this point. 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).

NACI has determined that there is insufficient (Grade I) evidence at this time to recommend the use of a two-dose Cervarix™ or Gardasil® schedule in females between 9 and 13 years of age.

While non-inferiority of antibody response to quadrivalent vaccine types has been demonstrated at 7 months following the initiation of a two-dose pediatric/adolescent regimen compared to a three-dose adult regimen of quadrivalent HPV vaccine, evaluation of study participants at months 18, 24 and 36 (including T-cell and B memory cell assays and clinical evaluation for HPV infection and cervical dysplasia) is still ongoing. Additional data will be assessed as they become available.

The immune response [or antibody titres] from a two-dose schedule of Cervarix™ also appears promising as it is non-inferior to the response from a three-dose schedule among females 9 to 25 years of age. The durability of this immune response following two doses has not been examined. Preliminary efficacy results suggest that less than three vaccine doses confer protection against persistent infection; however protection against cervical disease has not been examined. Further study is encouraged.

11. Because Cervarix™ and Gardasil® are not live vaccines, either can be administered to persons who are immunosuppressed as a result of disease or medications. However, 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. Cervarix™ and Gardasil® 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 woman is found to be pregnant after initiating the vaccination series, completion of the three-dose regimen should be delayed until after the pregnancy. If a vaccine dose has been administered during pregnancy, there is no indication for any intervention.

13. Cervarix™ and Gardasil® can be administered simultaneously with other adolescent vaccines (NACI Recommendation Grade A). Evidence from randomized-controlled trials indicates that both HPV vaccines are safe and immunogenic when co-administered with other adolescent vaccines. Administering all indicated vaccines together at a single visit increases the likelihood that adolescents and young adults will receive each of the vaccines on schedule. Each vaccine should be administered using a separate syringe at a different anatomic site.

VI. Research Priorities

The knowledge and infrastructure gaps in Canada related to how the HPV vaccine can be best used were the subject of a Canadian HPV Vaccine Research Priorities workshop in 2005. The results of the workshop were published in the CCDR: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/06vol32/32s1/index.html

The 10 highest-ranked research questions were:

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 on 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, what will be observed with cervical screening programs?

Since 2005, efforts have been underway to address many of these research questions. Research questions to address outstanding issues specifically related to the current NACI statement include the following:

- 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 Cervarix™ and Gardasil® 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.

Additional issues, such as the cost-effectiveness and feasibility of implementing NACI's recommendations in publicly-funded immunization programs must be considered by provinces and territories.

VII. Surveillance Issues

NACI encourages surveillance improvements in the following areas to support ongoing systematic collection, analysis, interpretation and timely dissemination of data for planning, implementation, evaluation, and evidence-based decision-making. High-quality surveillance for HPV vaccine program evaluation may answer many of the research questions outlined above.

Epidemiology

- Incidence/prevalence of infection/disease
- Distribution in high-risk populations (e.g. socioeconomic distribution and equity considerations)
- Determining the potential for changes to cervical cancer screening recommendations, (e.g. lengthened screening intervals, change in age at initiation / termination, etc.) requiring a coordinated surveillance efforts and linkage between vaccine registries, screening registries and STI surveillance

Laboratory

- HPV type distribution (e.g. monitor for type replacement, distribution of types in ethnic groups including aboriginal and immigrant communities)

Vaccine

- Immunization coverage
- Adverse events

Attitudes and behaviours

- Perceptions of vulnerability to disease
- Attitudes toward vaccination
- Sexual behaviour
- Cervical screening behaviour

Summary of Information Contained in this Naci Statement

The following table highlights key information for immunization providers. Please refer to the remainder of the Statement for details.

1. What • Basic information about the Disease • Basic information about the Vaccine	Human Papillomavirus (HPV) is a common virus that can infect different parts of the body. There are over 100 types of HPV. Some types of HPV are primarily sexually transmitted and can cause anal and genital warts and others lead to more serious consequences such as cervical, penile and anal cancers as well as certain cancers of the head and neck. In the absence of vaccination, it is estimated that 75 per cent of sexually active Canadians will have a sexually transmitted HPV infection at some point in their lives. Most HPV infections occur without any symptoms and go away without treatment over the course of a few years. However, in some people, HPV infections can persist. Persistent HPV infection with a cancer-causing type is the major cause of cervical cancer. There are two HPV vaccines approved for use in Canada. Gardasil® and Cervarix™ are indicated for the prevention of cervical adenocarcinoma *in situ* (AIS) and cervical cancer by protecting against dysplastic lesions caused by oncogenic HPV types 16/18. Gardasil® (HPV4) has been authorized in Canada since 2006 for the prevention of HPV types 6, 11, 16 and 18 related vulvar and vaginal cancers and their precursors, and genital warts in females 9 to 26 years of age. Since February 2010, Gardasil® was authorized to expand its indication to include: • Males 9 through 26 years of age for the prevention of infection caused by HPV types 6, 11, 16, and 18 and for genital warts (condyloma acuminata) caused by HPV types 6 and 11 • Women up to 45 years of age for the prevention of infection caused by HPV types 6, 11, 16 and 18 and related diseases including cervical, vulvar and vaginal cancers and their precursors,cervical adenocarcinoma in situ (AIS), and genital warts (condyloma acuminata). • Males and females 9 to 26 years of age for the prevention of anal intraepithelial neoplasia (AIN) grades 1, 2, and 3, anal cancer In February 2010, Cervarix™ (HPV2) was authorized for use in females 10 through 25 years for the prevention of cervical cancer caused by HPV types 16 and 18. Cervarix™ contains a novel proprietary adjuvant, AS04, designed to boost immunity. Long-term efficacy has been observed for up to 8.4 years after the first dose. Studies are ongoing to establish the duration of protection. Safety of the vaccine has been demonstrated. For more information on HPV, please visit: http://www.phac-aspc.gc.ca/std-mts/faq-eng.php#hpv

2. Who • Groups recommended to immunize	Gardasil® or Cervarix™ are recommended for the prevention of cervical cancer and AIS in: • females 9 through 26 years of age • females 15 through 26 years of age who have had previous Pap smear abnormalities, including cervical cancer and external genital warts. Gardasil® is recommended for the prevention of vulvar, vaginal, anal cancers and their precursors and anogenital warts in: • females 9 through 26 years of age. Gardasil® is recommended for the prevention of anal intraepithelial neoplasia (AIN), anal cancer, and anogenital warts in: • males between 9 and 26 years of age • men ≥9 years of age who have sex with men. Cervarix™ is not recommended for males at this time. Gardasil® or Cervarix™ may be administered to: • females over 26 years of age HPV vaccines are not recommended for: • females <9 years of age
3. How • Dose, schedule • Precautions, contraindications • Co-administration with other vaccines	Both vaccines are administered as three separate 0.5 mL doses intramuscularly in the deltoid region using slightly different schedules. Gardasil® is given as a 0, 2, and 6 month schedule. Cervarix™ is given as a 0, 1, and 6 month schedule. To avoid serious injury in the event of a syncopal episode after administration of vaccine, vaccinees should be observed for 15 minutes after vaccine administration. Neither vaccine should be administered to persons with a known history of hypersensitivity to any of the vaccine components. HPV2 (Cervarix™) in prefilled syringes is contraindicated for persons with anaphylactic latex allergy. Gardasil® can be administered at the same visit as other age-appropriate vaccines, such as hepatitis B, DTaP-IPV vaccine, conjugate meningococcal vaccine, and other adult/adolescent formulations of tetanus, diphtheria, and acellular pertussis vaccines. Cervarix™ can be administered at the same visit as other age-appropriate vaccines, such as hepatitis B, hepatitis A/B, the adolescent/adult formulation of Tdap, Tdap-IPV, and meningococcal conjugate vaccines. Each vaccine should be administered using a separate syringe at a different anatomical site.
4. Why "Counseling Points" for providers to emphasize with clients when discussing these recommendations	Gardasil® and Cervarix™ help protect females against infection and cervical cancer caused by HPV. HPV types 16 and 18 cause approximately 70% of cervical cancers. HPV vaccines will not treat HPV related diseases already present at time of vaccination, nor will it protect against diseases that are caused by non-vaccine types of HPV. If you are already infected with one vaccine type, the vaccine may provide protection against the other vaccine type(s). HPV vaccines, like other vaccines, may not fully protect all people who are vaccinated. Women must consult with their health care professional for regular cervical cancer screening (i.e. Pap tests) whether or not they receive an HPV vaccine.

Table 17. Summary of Evidence for NACI Recommendations

Evidence for efficacy in females 24 to 45 years						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings**	**Level of Evidence**	**Quality**
Munoz *et al.*[85]	Gardasil®	Randomized, double-blind, placebo controlled trial	n=3819 24 to 45 years of age; 38 international sites	*Per-protocol:* Efficacy against co-primary end-point (disease or infection related to HPV types 6/11/16/18) 90.5% (95% CI: 73.7-97.5) Efficacy against second co-primary end-point (disease or infection related to HPV types 16/18) was 83.1% (95% CI: 50.6-95.8) *Intention-to-treat:* Efficacy against co-primary end-point (disease or infection related to HPV types 6/11/16/18) 30.9% (95% CI: 11.1-46.5) Efficacy against second co-primary end-point (disease or infection related to HPV types 16/18) was 22.6% (95% CI: -2.9-41.9)	Level I	Good

Evidence for immunogenicity in females 24 to 45 years						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings**	**Level of Evidence**	**Quality**
Munoz et al.[85]	Gardasil®	Randomized, double-blind, placebo controlled trial	n=3819 24 to 45 years of age; 38 international sites	98% (n=1242) were anti-HPV type 6 seropositive; 98% (n=1238) anti-HPV type 11 seropositive; 99% (n=1264) were anti-HPV type 16 seropositive and 97% (n=1406) anti-HPV type 18 seropositive at month 7 following three doses of quadrivalent HPV vaccine (Gardasil®) at day 1, month 2 and month 6.	Level I	Good

Evidence for safety in females 24 to 45 years						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings**	**Level of Evidence**	**Quality**
Munoz et al.[85]	Gardasil®	Randomized, double-blind, placebo controlled trial	n=3819 24 to 45 years of age; 38 international sites	98% (n=1242) were anti-HPV type 6 seropositive; 98% (n=1238) anti-HPV type 11 seropositive; 99% (n=1264) were anti-HPV type 16 seropositive and 97% (n=1406) anti-HPV type 18 seropositive at month 7 following three doses of quadrivalent HPV vaccine (Gardasil®) at day 1, month 2 and month 6.	Level I	Good
Block et al.[145]	Gardasil®	Randomized, double-blind, placebo-controlled 3 doses at 0, 2 and 6 months Meta-analysis of Protocols 016, 018	n=21 480 females (9 to 26 years) and males (9 to 16 years) who received at least one dose of vaccine or placebo.	Injection-site AEs: -Most mild-moderate in intensity (78%). -Most common were pain (81.3%), swelling (24.2%) and erythema (23.6%) among vaccine recipients. -Significantly higher among vaccine versus placebo recipients; aluminum-containing (83% versus 77%, p<0.05) and non-aluminum containing (83% versus 49%, p<0.05). Systemic AEs: -Comparable between vaccine and placebo groups: headache (26% versus 28%), pyrexia (13% versus 11%) and nausea (6% versus 6%). Eight treatment-related adverse events (six in the vaccine group and two in the placebo group) 18 deaths, all unrelated	Level I	Good

Evidence for cross-protective efficacy against non-vaccine types in females ages 16 to 26 years						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings**	**Level of Evidence**	**Quality**
Brown *et al.*[86]	Gardasil®	Randomized, double-blind, placebo controlled trial Combined database of two phase III efficacy trials (FUTURE I and II)	n=17, 622 Exclusions: history of abnormal Pap test or treatment for genital warts	Reduction in incidence of HPV type 31/45 infection by 40.3% in vaccinated group (95% CI: 13.9-59.0); C1N1-3/AIS reduction of 43.6% (95% CI: 12.9-64.1) Reduction in incidence of HPV type 31/33/45/52/58 infection by 25.0% in vaccinated group (95% CI: 5.0-40.9); C1N1-3/AIS reduction of 29.2% (95% CI: 8.3-45.5) Efficacy for C1N2-3.AIS (high-grade lesions) associated with 10 non-vaccine types (31/33/35/39/45/51/52/56/58/59) was 32.5% (95% CI: 6.0-51.9)	Level I	Good
Wheeler *et al.*[87]	Gardasil®	Randomized, double-blind, placebo controlled trial Combined database of two phase III efficacy trials (FUTURE I and II)	n=17, 622	Significant reduction in rate of HPV types 31, 33, 45, 52 and 58 infection of 17.7% (95% CI: 5.1-28.7) and CIN1-3/AIS of 18.8% (95% CI: 7.4-28.9) Reduction in the rate of HPV type 31, 58, 59-related CIN1-3/AIS of 26.0% (95% CI: 6.7-41.4), 28.1% (95% CI: 5.3-45.6) and 37.6% (95% CI: 6.0-59.1) respectively	Level I	Good

Evidence for two-dose schedule in females						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings**	**Level of Evidence**	**Quality**
Dobson *et al.*[116]	Gardasil®	Randomized, double-blind, placebo controlled trial	Healthy girls 9 to 13 years, two doses of vaccine (n=259); Healthy girls 9 to 13 years (n=261), three doses of vaccine Females 16 to 26 years (n=310), three doses of vaccine	GMT Ratios (95% CI) were: (Group1/Group3, Group 1/Group 2, Group 2/Group 3) Anti-HPV type 16: 2.10 (1.62-2.73) 0.96 (0.74-1.24) 2.20 (1.69-2.85) Anti-HPV type 18: 1.84 (1.47-2.31) 0.70 (0.56-0.88) 2.62 (2.09-3.29) Anti-HPV type 6: 2.37 (1.78-3.14) 1.17 (0.88-1.56) 2.02 (1.52-2.67) Anti-HPV type 11: 1.86 (1.53-2.25) 1.11 (0.92-1.35) 1.67 (1.38-2.02)	Level I	Assessment pending peer-reviewed publication
HPV048	Cervarix™	Randomized Trial To assess immunogenicity and safety of a 2 vs 3 dose schedule	Females 9-25 years n=479	At Month 24, 2 doses of HPV-16/18 vaccine in girls 9–14y were non inferior to 3 doses of HPV-16/18 vaccine in women 15–25y, with corresponding GMTs (95% CI) of 1702 (1416–2045) vs 1865 (1505–2311) for HPV-16 and 702 (563–876) vs 728 (588–900) for HPV-18. The vaccine had a clinically acceptable safety profile in all groups up to Month 24.	Level I	Assessment pending peer-reviewed publication

Evidence for efficacy in males 9 to 26 years						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings**	**Level of Evidence**	**Quality**
Guiliano *et al*. [88]	Gardasil®	Randomized, double-blind, placebo-controlled Three doses at 0, 2 and 6 months 36 month follow-up (30.1 month mean for these results) Protocol 020	n=4065 males Heterosexual males 16 to 23 years (n=3463); MSM 16 to 26 years (n=602)	EGL (external genital lesion) efficacy 90.4 % (95% CI: 69.2-97.9) Type-specific EGL efficacy: Types 6, 11, 16, and 18: 84.3% (95% CI: 46.5-97.0), 90.9% (95% CI: 37.7-99.8), 100% (95% CI: 0-100), 100% (95% CI: <0-100) Efficacy against condyloma and PPPIN (penile/perianal/perineal intraepithelial neoplasia) 89.4% (95% CI: 65.5-97.9)	Level I	Good
Palefsky *et al*.[153]	Gardasil®			Efficacy against persistent infection: 85.6% (95% CI: 75.1-92.2) Efficacy against persistent infection from individual HPV types 6, 11, 16 and 18 88.0% (95% CI: 66.3-96.9), 93.4% (95% CI: 56.8-99.8), 78.7% (95% CI: 55.5-90.9), 96.0% (95% CI: 75.6-99.9) respectively. Efficacy against infection at ≥1 visit: 44.7% (95% CI: 31.5-55.6)	Level I	Assessment pending peer-reviewed publication

Evidence for immunogenicity in males 9 to 26 years						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings**	**Level of Evidence**	**Quality**
Mansi[90]	Gardasil®	Randomized, double-blind, placebo-controlled Three doses at 0, 2 and 6 months Meta-analysis of Protocols 016, 018, 020	Males 16 to 26 years (protocol 020); n=2025 Males 10 to 15 years (protocol 016); n=508 Males 9 to 15 years (protocol 018); n=839	PROTOCOL 020 Seroconversion (at month 7): Anti-HPV type 6 98.9% (98-99) Anti-HPV type 11 99.2% (98-100) Anti-HPV type 16 98.8% (98-99) Anti-HPV type 18 97.4% (96-98) GMTs (at month 7): Anti-HPV type 6 446.0 (422-474) Anti-HPV type 11 624.2 (594-656) Anti-HPV type 16 2402.5 (2271-2542) Anti-HPV type 18 402.2 (380-426) PROTOCOLS 016 and 018 Seroconversion (at month 7): Anti-HPV type 6 99.9% (99.4-100) Anti-HPV type 11 99.9% (99.4-100) Anti-HPV type 16 99.8% (99.2-100) Anti-HPV type 18 99.8% (99.2-100)	Level I	Assessment pending peer-reviewed publication
Block *et al*.[89]	HPV (types 6, 11, 16 and 18) L1 VLP vaccine (Gardasil®)	Age and gender stratified non-inferiority immunogenicity study (sub-study within randomized, double-blind, multi-dose study) Protocol V501-016	n=1529 (n=506, 10 to 15 year-old females; n=510, 10 to 15 year-old males; n=513, 16 to 23 year-old females)	≥99% seroconversion for all 4 HPV types in each group by month 7 GMTs were non-inferior and 1.7-2.7-fold higher in younger females and males compared to older females	Level I	Good
Reisinger *et al*.[115]	HPV (types 6, 11, 16 and 18) L1 VLP vaccine (Gardasil®)	Randomized, double-blind, placebo-controlled, multi-centre study Age and gender stratified Protocol V501-018	n=1781 healthy, sexually naive males and females aged 9 to 15 years	≥99% seroconversion for all 4 HPV types in each group by month 7 GMTs and seroconversion non-inferior in males ($p<0.001$) ≥91.5% seropositive at 18 months	Level 1	Good

Evidence for safety in males 9 to 26 years						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings**	**Level of Evidence**	**Quality**
Mansi [90]	Gardasil®	Randomized, double-blind, placebo-controlled Three doses at 0, 2 and 6 months Meta-analysis of Protocols 016, 018, 020	Males 16 to 26 years (protocol 020); n=4055 Males 10 to 15 years (protocol 016); n=508 Males 9 to15 years (protocol 018); n=839	Overall vaccine-associated adverse events (AE) 74%; 64% injection site pain (62%), erythema (17%) and swelling (14%), 18% vaccine-related systemic (headache (12%) and pyrexia (8%) Placebo AEs 64%; 53% injection site, 15% vaccine-related systemic 0.3% serious adverse events (n=9) (None vaccine-related.)	Level I	*Assessment pending peer-reviewed publication*
Block *et al.*[89]	HPV (types 6, 11, 16 and 18) L1 VLP vaccine (Merck)	Age and gender stratified non-inferiority immunogenicity study (sub-study within randomized, double-blind, multi-dose study) Protocol 016	n=1529 (n=506, 10 to 15 year-old females; n=510, 10 to 15 year-old males; n=513, 16 to 23 year-old females)	>97% of injection-site adverse events among males were mild to moderate Significantly more boys (13.8%) [and girls (12.8%)] than women (7.3%) reported fevers ≥37.8°C within 5 days of vaccination	Level I	Good
Block *et al.* [145]	Gardasil®	Randomized, double-blind, placebo-controlled Three doses at 0, 2 and 6 months Meta-analysis of Protocols 016, 018	n=21,480 females (9 to 26 years) and males (9 to 16 years) who received at least one dose of vaccine or placebo.	Injection-site AEs -Most mild-moderate in intensity (78%). -Most common were pain (81.3%), swelling (24.2%) and erythema (23.6%) among vaccine recipients - significantly higher among vaccine versus placebo recipients; aluminum-containing (83% versus 77%, p<0.05) and non-aluminum containing (83% versus 49%, p<0.05) Systemic AEs -comparable between vaccine and placebo groups: headache (26% versus 28%), pyrexia (13% versus 11%) and nausea (6% versus 6%). Eight treatment-related adverse events (six in the vaccine group and two in the placebo group) 18 deaths, all unrelated	Level 1	Good

Evidence for Efficacy, Immunogenicity in 15-25 year old females						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings**	**Level of Evidence**	**Quality**
HPV001 [97]	Cervarix™	Double blind, multi-centre, randomised, placebo-controlled trial To assess the efficacy of vaccine against incident and persistent infections	Females 15 to 25 years n=1113	In the ATP analyses, vaccine efficacy was: 91·6% (95% CI 64·5–98·0) against incident infection with HPV16/18; 100% (95% CI 47·0–100) against persistent infection with HPV16/18 In the ITT analyses, vaccine efficacy was: 95·1% (95% CI 63·5–99·3) against persistent cervical infection with HPV16/18; 92·9% (95% CI 70·0–98·3) against cytological abnormalities associated with HPV-16/18 infection	Level I	Good
HPV007 [103]	Cervarix™	Randomized, double-blind, placebo-controlled To assess efficacy, immunogenicity, safety up to 6.4 yrs	Females 15 to 25 years Initial study n=1113 Follow up study n=776	Vaccine efficacy: 95·3% (95% CI 87·4–98·7) against incident infection with HPV 16/18; 100% (81·8–100) against 12-month persistent infection; 100% (51·3–100) against CIN2+ for lesions associated with HPV-16/18 Antibody concentrations for HPV 16 and HPV 18 remained 12-fold higher or more than after natural infection. Participants reporting a SAE: -30 (8%) in the vaccine group -37 (10%) in the placebo group.	Level I	Good
HPV023 [128]	Cervarix™	Double blind study. To study the efficacy and immunogenicity of the vaccine up to 8.4 years.	Females 15 to 25 years n=433	All women were seropositive for HPV-16 and -18 antibodies by ELISA and PBNA, reaching a plateau ~18 months following first vaccination, with titres several fold above natural infection levels. Vaccine Efficacy (95% CI) against HPV-16/18-associated endpoints up to 8.4 years: 95.1% (84.6, 99.0) for incident infection; 100% (79.8, 100) for 6 month persistent infection; 100% (56.1, 100) for 12-month persistent infection; 94.6% (65.7, 99.9) for ≥LSIL; 100% (< 0, 100) for CIN2+	Level I	*Assessment pending peer-reviewed publication*
HPV008 PATRICIA [99]	Cervarix™	Double blind Randomized Study To assess vaccine efficacy in the final event-driven analysis.	Females 15 to 25 years n=18 644	Vaccine efficacy against CIN2+ associated with HPV-16/18 was 92·9% (96·1% CI 79·9–98·3) in the primary analysis. Vaccine efficacy against CIN2+ irrespective of HPV DNA in lesions was 30·4% (16·4–42·1) in the TVC and 70·2% (54·7–80·9) in the TVC-naive. Vaccine efficacy against CIN3+ were 33·4% (9·1–51·5) in the TVC and 87·0% (54·9–97·7) in the TVC-naive.		

Evidence for Immunogenicity, Safety in 10-14 year old females						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings**	**Level of Evidence**	**Quality**
HPV012 (133)	Cervarix™	Randomized trial To compare the immunogenicity and safety in early adolescent females to 15–25 year old females in whom vaccine efficacy has been demonstrated	Females 10 to 25 years n=773	Females 10-14 years and 15-25 years achieved 100% seroconversion for HPV 16 and 18. Participants 10–14 years of age were noninferior to those 15–25 years in terms of HPV 16 and 18 seroconversion rates and had approximately twice as high GMTs	Level II-1	Good
HPV013 (Medina et al)	Cervarix™	Observer-blinded, Randomized Controlled Trial To assess safety and immunogenicity in adolescent girls	Females 10 to 14 years n=2067	Up to month 7, 11 girls in the HPV-16/18 vaccine group reported 14 SAEs and 13 girls in the control group reported 15 SAEs. The difference in SAE incidence between groups was 20% (95% CI, _.78, 1.20). The incidence of solicited local and general symptoms up to 7 days postvaccination was moderately higher with the HPV-16/18 vaccine than with control. All girls seroconverted for both antigens after three doses of the HPV-16/18 vaccine. GMTs were 19,882.0 and 8,262.0 EU/mL for anti-HPV-16 and -18 antibodies, respectively, in initially seronegative girls.	Level I	Good
HPV013	Cervarix™	Multicentric, double-blinded, randomized, controlled study To evaluate safety and immunogenicity. Havrix (HAV) was used as a control vaccine.	Females 10 to 14 years n=741	Between Month 0 and Month 12, SAEs were reported for 22 (2.1%) and 23 (2.2%) subjects in the HPV and HAV groups, respectively. Between Month 12 and Month 18, SAEs were reported for 7 (1.1%) and 2 (0.3%) subjects in the HPV and HAV groups, respectively; from Month 18 to 24, SAEs were reported for 8 (1.3%) and 5 (0.9%) subjects in the HPV and HAV groups, respectively. From Month 24 to 36, SAEs were reported for 10 (1.7%) subjects and from Month 36 to 48, SAEs were reported for 15 (2.6%) subjects in the HPV Group. In the HPV Group, at Month 7, all subjects were seropositive for anti-HPV-16 and for anti-HPV-18 with GMTs of 20018.1 and 8359.4, respectively; at Month 48, all subjects were seropositive for anti-HPV-16 and for anti-HPV-18 with GMTs of 2395.8 and 885.6, respectively.	Level I	*Assessment pending peer-reviewed publication*

Evidence for Immunogenicity, Safety in 26-55 year old females						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings**	**Level of Evidence**	**Quality**
HPV014 (120)	Cervarix™	Non-randomized, open-label, age-stratified Study To assess immunogenicity and safety of vaccine in women aged 26–55 years compared with women aged 15–25 years	Females 15 to 55 years n=666	At Month 2, all initially seronegative women became seropositive for both HPV 16 and 18. At Month 7, HPV-16 GMTs (95% CI) were: in 15-25 year olds: 7908.4 (6874.0–9098.5) ; in 26-45 year olds: 4029.2 (3402.7–4771.0); in 46-55 year olds: 2566.8 (2181.2–3020.6) At Month 7, HPV-18, GMTs (95% CI) were: in 15-25 year olds: 3499.3 (3098.7–3951.6) ; in 26-45 year olds: 1837.3 (1602.1–2107.0) ; in 46-55 year olds: 1313.0 (1145.6–1504.9) Incidence of local symptoms (within 30 days) lower in the 46–55 year-old group (69.2% versus 81.6% [26–45] and 85.7% [15–25])	Level II-1	Good

Evidence for Immunogenicity, Safety in Males						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings**	**Level of Evidence**	**Quality**
HPV011 (132)	Cervarix™	Observer-blind randomized study To evaluate the immunogenicity and safety in males.	Males 10 to 18 years n=270	All initially seronegative seroconverted for HPV-16 and 18 at month 2. At month 7, all subjects were seropositive, and the HPV-16 and -18 antibody levels were four- and twofold higher than at month 2. Reactogenicity profiles of the Cervarix™and HBV (control) vaccines were similar, except that pain and swelling at the injection site were more common in the Cervarix™ group.	Level I	Good

Evidence for immunogenicity and safety of a fourth dose of vaccine in young adult females						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings**	**Level of Evidence**	**Quality**
HPV024	Cervarix™	Open, multicentric study with 2 treatment groups (4 dose – HPV-4D vs 3 dose—HPV-3D) To assess the immunogenicity and safety of a 4th HPV dose in young adult women	Females 10 years of age and older Mean age: 27 years n=115	6.8 years after the initial 3-dose vaccination course, all subjects in the HPV-4D Group were seropositive for both HPV-16 (GMT value = 720.7) and HPV-18 antibodies (GMT value = 502.9). In the HPV-3D Group, prior to the first vaccination, 28.9% and 26.7% of subjects were seropositive for antibodies against HPV 16 (GMT value = 8.6) and HPV-18 (GMT value =5.9), respectively (natural infection). Seven days after the fourth dose, all subjects in the HPV 4D Group were seropositive for antibodies against HPV-16 (GMT value = 5894.9) and HPV-18 (GMT value = 3916.2). One month after receiving a 4th dose of the HPV vaccine, all subjects in the HPV-4D Group were seropositive for antibodies against HPV-16 (GMT value = 15410.7) and HPV-18 (GMT value = 8362.7). Seven days after the first dose, 66.7% and 57.8% of subjects in the HPV 3D were seropositive for antibodies against HPV-16 (GMT value = 67.9) and HPV-18 (GMT value = 20.7), respectively. One month after the first dose, all subjects in that group were seropositive for antibodies against both antigens (GMT value for HPV-16 = 1231.1 and for HPV-18 = 442.0). During the post vaccination follow-up period, 24 (36.9%) subjects in HPV-4D Group and 25 (50.0%) subjects in HPV-3D Group reported unsolicited AEs.	Level II-1	*Assessment pending peer-reviewed publication*

Evidence for viral clearance in females already infected with HPV						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings**	**Level of Evidence**	**Quality**
HPV009 [101]	Cervarix™	Randomized trial To determine whether vaccination increases the rate of viral clearance in women already infected with HPV	Females 18 to 25 years n=2189	No evidence of increased viral clearance at 6 or 12 months in the group who received HPV vaccine compared with the control group. Clearance rates for HPV-16/18 infections: -at 6 months: 33.4% (82/248) in the HPV vaccine group and 31.6% (95/298) in the control group (vaccine efficacy for viral clearance, 2.5%; 95% CI,–9.8%to 13.5%). -at 12 months: 48.8% (86/177) in the HPV vaccine group and 49.8% (110/220) in the control group (vaccine efficacy for viral clearance,–2.0%;95%confidence interval,–24.3%to 16.3%).	Level I	Good

Evidence for co-administration with other vaccines						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings**	**Level of Evidence**	**Quality**
HPV018	Cervarix™	Randomized, open, multicentre study To compare vaccine co-administered with Boostrix® vaccine (Tdap) and/or Menactra™ vaccine (MCV4) to administration of these vaccines alone	Females 11 to 18 years n=1283	Criteria for non-inferiority were met for all of the co-primary immunogenicity variables assessing co-administration of Tdap with HPV vaccine and MCV4 with HPV vaccine one month post-vaccination During the 30-day follow-up period after vaccination, unsolicited adverse events were reported by 118 (54.9%) subjects in the HPV Group, 108 (50.9%) in the HPV + Tdap/ MCV4 Group, 121 (56.5%) in the HPV + MCV4/ Tdap Group, 119 (55.6%) in the HPV + MCV4+ Tdap, 122 (57.0%) in the Tdap /HPV Group and 127 (59.3%) in the MCV4/HPV Group.	Level I	*Assessment pending peer-reviewed publication*
HPV026 (Leroux-Roels et al., 2011)	Cervarix™	Randomized, controlled, open-label study To assess immunogenicity and safety of the hepatitis B vaccine given in an accelerated schedule co-administered with Cervarix™	Females 20 to 25 years n=152	One month after the third dose of hepatitis B vaccine, hepatitis B seroprotection rates (titer of >10 mIU/ml) were 96.4% (CI, 87.5 to 99.6) and 96.9% (CI, 89.2 to 99.6) in the HepB_HPV and HepB groups, respectively, in women initially seronegative for anti-hepatitis B surface antigen (HBs) and anti-hepatitis B core antigen (HBc). Corresponding GMTs of anti-HBs antibodies were 60.2 mIU/ml (CI, 40.0 to 90.5) and 71.3 mIU/ml (CI, 53.9 to 94.3). Anti-HBs antibody titers rose substantially after the fourth dose of hepatitis B vaccine. All women initially seronegative for anti-HPV-16 and anti-HPV-18 antibodies seroconverted after the second HPV-16/18 vaccine dose and remained seropositive up to 1 month after the third dose. Both vaccines were generally well tolerated, with no difference in reactogenicity between groups.	Level I	Good

Evidence for co-administration with other vaccines						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings**	**Level of Evidence**	**Quality**
HPV029	Cervarix™	Open, randomized controlled, multicentre study with 3 parallel treatment groups To evaluate immunogenicity and safety of HPV vaccine when co-administered combined hepatitis A and B vaccine (HAB), Twinrix® Paediatric, compared to the administration of these vaccines alone	Females 9 to 15 years n=812	Criteria for non-inferiority met for all of the co-primary immunogenicity variables assessing coadministration of HAB vaccine with HPV vaccine At Month 7, the percentage of initially seronegative subjects with anti-HPV-16 antibody titres 8 EL.U/mL was 99.6% in the HPV + HAB Group and 100% in the HPV Group, with antibody GMTs of 22993.5 EL.U/mL in the HPV + HAB Group and 26981.9 EL.U/mL in the HPV Group. The percentage of initially seronegative subjects with anti-HPV-18 antibody titres_ 7 EL.U/mL was 99.6% in the HPV + HAB Group and 100% in the HPV Group, with antibody GMTs of 8671.2 EL.U/mL in the HPV + HAB Group and 11182.7 EL.U/mL in the HPV Group. During the active phase of the study (up to Month 7), unsolicited AEs were reported within the 30-day post-vaccination period in 83 (30.5%) subjects in the HPV + HAB Group, 96 (35.6%) subjects in the HPV Group and 83 (30.6%) subjects in the HAB Group; SAEs were reported for 2 (0.7%) subjects in the HPV + HAB Group, 3 (1.1%) subjects in the HPV Group and 4 (1.5%) subjects in the HAB Group.	Level I	*Assessment pending peer-reviewed publication*
HPV042	Cervarix™	Open, randomized, controlled multicentre study with 3 parallel groups. To evaluate immunogenicity and safety of Boostrix® Polio (dTpa-IPV) vaccine co-administered with HPV vaccine compared to the administration of the vaccines alone	Females 10 to 18 years n=751	At Month 7, non-inferiority of Cervarix™ when co administered with dTpa-IPV vaccine at Month 0 compared to Cervarix™given alone at Month 0 was demonstrated in terms of anti HPV-16 and anti HPV-18 GMT values. None of the SAEs reported during the whole course of the study were considered to be causally related to the study vaccination. No fatal SAEs were reported throughout the study	Level I	*Assessment pending peer-reviewed publication*

Evidence for Immunogenicity of Cervarix™ vs Gardasil®						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings**	**Level of Evidence**	**Quality**
HPV010 (117, 136)	Cervarix™ vs Gardasil®	Observer-blind study To compare the immunogenicity of these vaccines 12 months after a third dose (Month 18).	Females 18 to 45 years n=1106	GMTs of serum neutralizing antibodies ranged from 2.3–4.8-fold higher for HPV-16 and 6.8–9.1-fold higher for HPV-18 after vaccination with Cervarix™ compared with Gardasil®, across all age strata. In the TVC, Cervarix™ induced significantly higher serum neutralizing antibody titers in all age strata ($p < 0.0001$). Incidence of unsolicited adverse events was comparable between vaccinated groups; incidence of solicited symptoms was generally higher after Cervarix™, with injection site reactions being most common.	Level I	*Good*

Table 18. Levels of Evidence Based on Research Design

I	Evidence from randomized controlled trial(s).
II-1	Evidence from controlled trial(s) without randomization.
II-2	Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group using clinical outcome measures of vaccine efficacy.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

Table 19. Quality (internal validity) Rating of Evidence

Good	A study (including meta-analyses or systematic reviews) that meets all design- specific criteria* well.
Fair	A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion* but has no known "fatal flaw".
Poor	A study (including meta-analyses or systematic reviews) that has at least one design-specific* "fatal flaw", or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.

* General design specific criteria are outlined in Harris *et al.*, 2001.[1]

Table 20. NACI Recommendation for Immunization – Grades

A	NACI concludes that there is **good** evidence to recommend immunization.
B	NACI concludes that there is **fair** evidence to recommend immunization.
C	NACI concludes that the existing evidence is **conflicting** and does not allow making a recommendation for or against immunization; however other factors may influence decision-making.
D	NACI concludes that there is **fair** evidence to recommend against immunization.
E	NACI concludes that there is **good** evidence to recommend against immunization.
I	NACI concludes that there is **insufficient** evidence (in either quantity and/or quality) to make a recommendation, however other factors may influence decision-making.

[1] Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 2001;20:21-35.

List of Abbreviations

Abbreviation	Term
AAHS	amorphous aluminum hydroxyphosphate sulfate
AE	adverse event
AGW	anogenital warts
AHR	adjusted hazard ratio
AIN	anal intraepithelial neoplasia
AIS	adenocarcinoma *in situ*
(A)OR	(adjusted) odds ratio
ATP	according-to-protocol
BC	British Columbia
CCDR	Canada Communicable Disease Report
CI	confidence interval
CIN	cervical intraepithelial neoplasia
cLIA	competitive Luminex immunoassay
DNA	deoxyribonucleic acid
DTaP-IPV	diphtheria, tetanus, acellular pertussis, inactivated polio vaccine
EGL	external genital lesion
ELISA	enzyme-linked immunosorbent assay
HAART	highly active antiretroviral therapy
HIM	HPV in Men study
HITCH	HPV Infection and Transmission among Couples through Heterosexual activity study
HIV	human immunodeficiency virus
HM	heterosexual male
HPV	human papillomavirus
HR	high risk
HRQoL	health-related quality of life
HSV	herpes simplex virus
IARC	International Agency for Research on Cancer
ICD-O-3	International Classification of Diseases for Oncology Third Edition
ITT	intention-to-treat
LEEP	Loop Electrosurgical Excision Procedure
MPL	3-O-desacyl-4'-monophosphoryl lipid A
MSC	medically significant conditions
MSM	men who have sex with men
Nab	neutralizing antibody
NACI	National Advisory Committee on Immunization
NHANES	National Health and Nutrition Examination Survey
NOAD	new onset autoimmune disease
NOCD	new onset chronic disease
NRT	naïve to the relevant type
PCR	polymerase chain reaction

PHAC	Public Health Agency of Canada
PPE	per-protocol population
PPPIN	penile/perianal/perineal intraepithelial neoplasia
PRR	proportional reporting ratio
QALY	quality-adjusted life years
RR	relative risk
SAE	serious adverse events
SCC	squamous cell carcinoma
SEER	Surveillance, Epidemiology and End Results Registry
SFMHS	San Francisco Men's Health Study
STI	sexually transmitted infection
Tdap	tetanus, diphtheria, acellular pertussis vaccine
TNFα	tumor necrosis factor α
TVC	total vaccinated cohort
TVC-E	total vaccinated cohort-efficacy population
TVC-N	total vaccinated cohort-naïve population
US	United States
VAERS	Vaccine Adverse Event Reporting System
VaIN	vaginal intraepithelial neoplasia
VE	vaccine efficacy
VIN	vulvar intraepithelial neoplasia
VLP	virus-like particle

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(Footnotes)

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