

# Recommendations for Human Papillomavirus Vaccination

Provincial Infectious Diseases Advisory Committee on  
Immunization

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This document was prepared for the Provincial Infectious Diseases Advisory Committee on Immunization (PIDAC-I). PIDAC-I is a multidisciplinary scientific advisory body that provides evidence-based advice to the Ontario Agency for Health Protection and Promotion (Public Health Ontario) regarding immunization. PIDAC-I's work is guided by the best available evidence and updated as required.

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# Background

The quadrivalent human papillomavirus (HPV) vaccine, Gardasil<sup>®</sup>, was authorized for use in Canada in 2006 and the bivalent vaccine, Cervarix<sup>™</sup>, in 2010. There have been two National Advisory Committee on Immunization (NACI) statements pertaining to HPV vaccines, the first published in February 2007 and the second in January 2012<sup>1,2</sup>. In December 2007, the Canadian Immunization Committee (CIC) released programmatic recommendations for HPV vaccine<sup>3</sup>. The objective of the CIC report was to provide recommendations to federal/provincial/territorial immunization program decision-makers with evidence-based information to facilitate program planning in their jurisdictions. The national goal of HPV immunization programs, as articulated in the CIC report, is to decrease the morbidity and mortality associated with cervical cancer, its precursors and other HPV-related cancers in women in Canada, through combined primary prevention (immunization) and secondary prevention (screening) programs.

In August 2007, the province of Ontario announced plans to implement a publicly-funded, school-based HPV immunization program using Gardasil<sup>®</sup> vaccine, beginning in the 2007-2008 school year. The Ontario program is locally administered by its 36 local public health agencies. Grade 8 girls (approximately 13-14 years of age) are eligible for publicly-funded vaccine, using a 3-dose schedule, administered over a 4 to 6 month period. The provincial program targets a single grade cohort and a catch-up component was not included. However, if a grade 8 girl receives at least one dose, she may complete the vaccine series while she is in her grade 9 year. This is referred to as extended eligibility.

## Licensed Indications

From a provincial and regulatory perspective, the licensed indications of the products are important considerations. Health Canada has authorized use of Gardasil<sup>®</sup> in males and both Gardasil<sup>®</sup> and Cervarix<sup>™</sup> in females, but their indications and upper age limit differ:

- Gardasil<sup>®</sup> 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 anogenital warts (AGW) (condylomata acuminata).
- Gardasil<sup>®</sup> 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 AGWs.
- Gardasil<sup>®</sup> 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
- Cervarix<sup>™</sup> 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.

Both vaccines are licensed to be given in a three-dose series. Whereas both vaccines are indicated to protect against cervical cancers, only Gardasil<sup>®</sup> has a licensed indication of preventing vaginal, vulvar, and anal cancers, as well as AGWs; neither vaccine has been shown to prevent oropharyngeal cancers or recurrent respiratory papillomatosis (RRP) and therefore prevention of these conditions are not included within the licensed indications. However, it is important to note that it is biologically plausible that both vaccines will offer protection against other disease outcomes associated with the two or four genotypes contained in the vaccines.

# Summary of recommendations made by NACI in the 2012 update on HPV vaccines<sup>2</sup>

In January 2012, NACI made 13 recommendations for HPV vaccine use<sup>2</sup>. These pertain to the use of both bivalent (Cervarix™) and quadrivalent (Gardasil®) vaccine, as well as use in both males and females. Prior to examining the recommendations, it is important to note that NACI is making recommendations for the optimal use of vaccines and does not consider economic assessments or other programmatic considerations. Programmatic recommendations are under the purview of the CIC, which is expected to release HPV vaccine recommendations in the summer of 2012.

Five of the NACI recommendations pertain to HPV vaccine use in females<sup>2</sup>. The key recommendations are:

1. HPV vaccine (Cervarix™ or Gardasil®) is recommended for females between 9 and 13 years of age
2. HPV vaccine (Cervarix™ or Gardasil®) is recommended for females between 14 and 26 years of age
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.
4. HPV vaccine (Cervarix™ or Gardasil®) may be administered to females over 26 years of age (NACI Recommendation Grade A (Gardasil®) Grade B (Cervarix™).
5. HPV vaccine (Cervarix™ or Gardasil®) is not recommended in females <9 years of age.

Four of the NACI recommendations pertain to males<sup>2</sup>:

1. 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.
2. Gardasil® is recommended in males between 9 and 26 years of age for the prevention of penile, perianal and perineal intraepithelial neoplasias and associated cancers.
3. Gardasil® is recommended in males who have sex with males (MSM) ≥9 years of age.
4. Cervarix™ is not recommended in males at this time.

NACI stated that the following issues may be considered by provinces and territories regarding inclusion of males in publicly-funded vaccination programs<sup>2</sup>:

- 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.
- 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.
- While current models predict that addition of males to a routine HPV vaccination program would prevent additional cases of genital warts and cervical cancer among females to varying degrees, this is based on assumptions that such transmission from males to females will be reduced, rather than observational data.
- In addition, cost effectiveness needs consideration. Provinces and territories will need to compare the impact of vaccinating males with that of vaccinating additional female cohorts.
- While not directly comparable, lessons learned from gender-targeting of other vaccines should be considered (e.g., rubella). Factors such as vaccine refusal, cost and weaknesses in vaccine delivery systems may support a gender-neutral (universal) policy to adequately control disease.

One NACI recommendation pertains to the two-dose schedule<sup>2</sup>:

1. 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.

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 vaccine, the two-dose study<sup>4</sup> is ongoing and further follow-up data are needed, including evaluation of immune response at 36 months. NACI emphasized that the efficacy, effectiveness, and long-term immunogenicity of a two-dose HPV vaccine schedule for adolescents (females and males), as well as the durability of immune response (antibody titres and immune memory) and long-term efficacy of the two-dose schedule against infection and disease outcomes need to be determined<sup>2</sup>.

The remaining three recommendations were general<sup>2</sup>:

1. 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 have not been fully determined in this population and thus individuals may not derive benefit from these vaccines.
2. Cervarix™ and Gardasil® are not recommended for use in pregnancy.
3. Cervarix™ and Gardasil® can be administered simultaneously with other adolescent vaccines.

## Comparison of the two HPV vaccines

The major differences between the two HPV vaccines are that Gardasil® protects against four genotypes (types 6, 11, 16 and 18) and Cervarix™ protects against two (types 16 and 18), and that Cervarix™ uses a proprietary adjuvant (ASO4) whereas Gardasil® uses alum. NACI has indicated that the choice of vaccine depends on importance of AGW protection and that if this is important, HPV4 vaccine is recommended, whereas if the programmatic goal is prevention of HPV type 16 and 18-related cancers, either vaccine may be used<sup>2</sup>. The two vaccines both have similar efficacy. Comparing the immunogenicity profiles of the two products is complicated by the fact that serologic correlates of immunity to HPV infection are unknown and that the serologic assays developed by both manufacturers to assess immune response are proprietary and not

comparable. In addition, data suggest that the immune response in the mucosa may play an important role in HPV infection and it is not clear how mucosal antibodies correlate to serum antibodies<sup>5</sup>. Despite these issues, it is important to note that there has been a head to head trial funded by GSK (manufacturer of Cervarix™), which found that the geometric mean titers (GMTs) were 2.4-5.8-fold higher for HPV-16 and 7.7-9.4-fold higher for HPV-18 with the bivalent vaccine compared to the quadrivalent vaccine, up to 24 months after receipt of vaccine<sup>6</sup>. These data suggest that the immune response may be greater for Cervarix™; however, the clinical significance of these findings is unknown. NACI has emphasized that the clinical significance of the differences in the immune profiles of the two vaccines is unknown and that a head-to-head comparison, with a primary outcome of cancer protection, is warranted<sup>6</sup>.

The 2012 NACI HPV vaccine statement reviews cross protection data from both the bivalent and quadrivalent vaccine in detail (Table 2). Both vaccines have demonstrated cross protection, particularly against genotypes 31 and 45, the third and fifth most common HPV genotypes<sup>7</sup>. From a regulatory standpoint, neither vaccine is authorized to provide protection against genotypes not included in the vaccine; however it is likely that both vaccines will offer some additional protection against these genotypes and that the cross protection offered by Cervarix™ may be superior to that of Gardasil®. NACI has emphasized that the long-term impact of cross protection on disease outcomes following either vaccine should be a research priority.

## Table 2: Vaccine efficacy for related genotypes

CIN 2 +	Cervarix™ (95% CI)	Gardasil® (95% CI)
HPV 31/45		
• Infection	100 (82.2, 100)*	40.3% (13.9, 59.0)
• CIN1-3/AIS		43.6% (12.9, 64.1)
5 non-VT CIN2+ (31/33/45/53/58)	68.2% (40.5, 84.1)	
10 non-VT CIN2+ (31/33/35/39/45/51/52/53/56/58/59)	66.1% (37.3, 82.6)	32.5% (6.0, 51.9)

\*CIN2+ rather than CIN1

# Vaccine Coverage

Provincial HPV vaccination coverage during the first three years of the program was 51% in year one (2007/08), 58% in year two (2008/09) and 59% in year three (2009/10). This coverage is likely an underestimate, as not all local public health agencies were able to include the extended eligibility component in their coverage estimates. Although coverage has increased over time, it is below the objective set by CIC of 80% within two years of program implementation.

## Economic Evaluations

In January 2012, Tully et al. published a cost-utility analysis of screening and immunization with the bivalent vaccine (Cervarix™) for the Canadian setting from the Ministry of Health perspective<sup>8</sup>. A dynamic model was used to allow herd immunity to be captured. A compartmental HPV transmission model was linked to a natural history model of cervical cancer to evaluate the cost-effectiveness of catch-up HPV immunization programs in Ontario. With respect to immunization, the authors found that the following strategies were cost-effective versus the chosen comparator:

- Immunizing 80% of 12-year old females is cost-effective compared to no immunization
- Adding a school-based catch-up program is cost-effective compared to no immunization
- Both catch-up programs (school-based and clinic-based) are cost-effective compared to no catch-up

In terms of applicability of this paper to the Ontario context, the authors assessed the school-based vaccination program at age 12 years. In Ontario, we are vaccinating girls in grade 8, which would actually be girls at approximately 13-14 years of age, but it is expected the results would be applicable in this context. It is however important to note that an outstanding PIDAC-I recommendation, for the grade of vaccination to be moved to grade 7, would be consistent with this analysis. In Ontario, vaccine coverage from the school-based program is lower than the 80% used in the model; however, the authors did conduct a sensitivity analysis with lower vaccine coverage values (including 60% coverage) and the conclusions held. Although the analysis was based on the bivalent vaccine, the results would be applicable to the quadrivalent vaccine if equal costs were applied (i.e., \$90 per dose) and assuming similar vaccine efficacy. As the public procured price for the vaccine is unknown, we are unable to comment on the applicability of the cost used in this analysis from a Ministry of Health payer perspective.

It is noteworthy that comparator 3, school-based vaccination with school-based catch-up, which was found to be cost effective, is also a modification of another outstanding PIDAC-I recommendation: that girls should remain eligible for HPV vaccination even if it was not received during their grade 8 year. As the program was initiated in the 2007/08 school year, the first cohort of HPV vaccinated girls would currently be in grade 12. This is the last year we could have accessed these girls through a school-based campaign.



# Comparative cost effectiveness of the two vaccines

At the November 2011 PIDAC-I meeting, an economic assessment of the two HPV vaccines was presented. The summary of this assessment was that Cervarix™ may be equally cost-effective as Gardasil® under the following scenarios:

1. Assumptions which favour Cervarix™ (both vaccines protect against all related cancer end points): The price of Cervarix™ should be 22% to 43% lower than Gardasil®.
2. Assumptions which do not favour Cervarix™ (both vaccines protect only against licensed end points (cervical cancer for Cervarix™; cervical, vaginal, vulvar, and anal cancer as well as warts and mild smears for Gardasil®): The price of Cervarix™ should be 54% to 77% lower than Gardasil®.

Note: scenario two consists of the authorized indications for each of the vaccines. It should be further noted that the relative price differential was calculated based on a 3-dose schedule and local cost-effectiveness thresholds. The relative price reduction would be different for different vaccination schedules (e.g. 2-dose), vaccine costs and different cost-effectiveness thresholds.

## PIDAC-I Recommendations

PIDAC-I will be considering HPV vaccine in two stages: the first will focus on the current HPV vaccination program. Once the CIC recommendations are released (expected in the summer of 2012), PIDAC-I will more fully consider the male vaccination issue. PIDAC-I would like the Ministry of Health and Long Term Care (MOHLTC) to consider the following four recommendations:

1. PIDAC-I would like to reaffirm their outstanding PIDAC-I HPV vaccine recommendations:
  - Move school-based HPV vaccination from grade 8 to grade 7
  - Implement a “once eligible, always eligible” policy for HPV vaccine

Both of these recommendations were made directly to the MOHLTC, prior to the transition of PIDAC-I to Public Health Ontario.

2. Implement a one-time high school catch-up program in the 2012/13 school year. Although we will have missed the first cohort of girls eligible for the grade 8 program (i.e., those vaccinated in 2007/08 school year), there is still an opportunity for other girls to benefit from this program, given that vaccine coverage is not ideal. If a “once eligible, always eligible” policy is implemented (as per above PIDAC-I recommendation), girls in high school would have another opportunity to receive the vaccine series through the catch-up program. This change would likely result in higher coverage than referring unvaccinated girls to their primary care providers. In addition, these girls should be able to provide their own consent to receive the vaccine. A high school catch-up campaign may also have a spin off promotional effect to raise HPV coverage in the grade 8 program (or grade 7 program if a switch is made).

3. Publicly-fund Gardasil® for men who have sex with men or males who identify as homosexual up to the age of 26 years. A variety of delivery mechanisms should be considered to reach this target population (e.g. sexual health clinics, primary care practices)
4. Continue to use Gardasil® for women, as it offers protection against both anogenital warts, as well as HPV-related malignancies, unless the cost of Cervarix™ meets the criteria of the economic analysis by PHO and if the use of Cervarix™ would result in additional female cohorts eligible to receive the vaccine. If that situation should develop, the issue of the importance to the health system and the population of preventing AGW needs to be considered

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