RECOMMENDATIONS ON A HUMAN PAPILLOMAVIRUS IMMUNIZATION PROGRAM

CANADIAN IMMUNIZATION COMMITTEE

December 2007

Catalogue No. HP40-29/2008E-PDF
ISBN 978-0-662-48433-2

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Executive summary

The Canadian Immunization Committee's (CIC) *Recommendations on a Human Papillomavirus* (HPV) *Immunization Program* is the Committee's first statement on immunization programs. This statement provides the analysis needed for the implementation of routine HPV immunization programs. Its objective is to provide recommendations to federal/provincial/territorial (F/P/T) immunization program decision-makers with evidence-based information to facilitate program planning in their jurisdictions. Provinces and territories are responsible for the delivery of immunization programs and will consider their own set of circumstances in making decisions about the implementation of HPV immunization programs.

The work of the CIC represents a significant step forward for immunization program planning at the pan-Canadian level. . Achieving consensus on goals, targets and routine programs at the start of program implementation has not been done at the national level in the past.

The CIC recommendations on HPV vaccine programs are based on an analysis of the epidemiology of HPV, vaccine characteristics, Canadian disease modeling and economic analyses, as well as on the feasibility and acceptability of HPV immunization programs. The first quadrivalent HPV vaccine was licensed in Canada in July 2006. As new knowledge and new vaccines become available, the recommendations will be reviewed and updated as needed.

The national goal of HPV immunization programs 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.

The recommendations on reduction in disease incidence are as follows:

1. To reduce by 60% the incidence of cervical intraepithelial neoplasia (CIN) 2/3 caused by HPV 16/18 in Canada within 20 years of the introduction of a HPV vaccination program.
2. To reduce by 60% the incidence of cervical cancers (and other HPV-related cancers) caused by HPV 16/18 in Canada within 30 years of the introduction of an HPV vaccination program.
3. To reduce by 60% the mortality due to cervical cancer caused by HPV 16/18 in Canada within 35 years of the introduction of an HPV vaccination program.

CIC recommends school-based HPV vaccination of one female cohort to be implemented in all Canadian provinces and territories:

(a) To immunize 80% of school-aged girls in either grade 4, 5, 6, 7 or 8 with the required doses of the HPV vaccine within 2 years of program introduction.

(b) To immunize 90% of school-aged girls in either grade 4, 5, 6, 7 or 8 with the required doses of the HPV vaccine within 5 years of program introduction.

The Canadian disease modeling and economic analyses indicate that vaccinating a grade 4, 5, 6, 7 or 8 schoolgirl cohort is a cost-effective strategy. Jurisdictions should consider their own population characteristics, such as the age at sexual debut and the ability to reach girls at different ages to achieve maximum vaccine coverage, when deciding on their routine programs.

CIC also indicates that jurisdictions that wish to and are able to consider catch-up programs could proceed with the inclusion of additional female cohorts. Particular efforts should be undertaken to

achieve high vaccine coverage for routine programs in hard-to-reach and high-risk populations. Catch-up strategies could also be extended to these populations.

Currently, there are inadequate epidemiological data on the general incidence and impact of anogenital condylomas (warts); there are also no data on the effectiveness of HPV vaccines in males, and the vaccine is not authorized for sale in males. Therefore, the HPV immunization program is recommended for girls and women for cervical cancer prevention only at this time.

Routine HPV immunization programs for the prevention of cervical cancer have been implemented in a number of industrialized countries, including the United States, Australia and western European countries. In general, routine immunization programs target primarily females before adolescence and before debut of sexual activity, with an age range from 9 to 17 years. HPV vaccines are currently licensed in more than 60 countries.

Both the National Advisory Committee on Immunization (NACI) and the CIC have deemed that there is sufficient evidence to support the implementation of routine HPV immunization programs as part of cervical cancer prevention programs in Canada, while recognizing that there are important research questions that need to be further addressed after implementation. Both committees stress that HPV immunization does not replace the need for fully implemented, organized cervical cancer screening programs and the promotion of safe sex practices.

1. Background

The Canadian Immunization Committee (CIC) is the federal/provincial/territorial (F/P/T) body that provides leadership in immunization by giving advice and recommendations on implementation of the National Immunization Strategy (NIS) and issues affecting immunization. The CIC is part of the Pan-Canadian Public Health Network (PHN), which reports to the Public Health Network Council through the Communicable Disease Control Expert Group.

F/P/T immunization programs need to assess key vaccines coming onto the Canadian market and the feasibility of introducing them in the publicly funded system. The CIC's mandate includes national collaboration on immunization program planning, one of the 10 components of the NIS. The objectives of a national process for immunization program planning are to minimize duplication of effort and to move towards harmonization of immunization schedules across the country. In December 2005 the PHN identified human papillomavirus (HPV) vaccine as a priority in program planning. It agreed to move forward on the overall evaluation of a candidate immunization program for the HPV vaccine using the analytical framework for immunization programs in Canada developed by Erickson, De Wals and Farand[(1)]. Consensus was reached on the need for F/P/T collaboration and consistency in the assessment of new and future immunization programs and the development of business cases to be proposed in Canadian jurisdictions.

Vaccines are authorized for sale in Canada after rigorous scientific review and testing for their quality, safety and effectiveness. Health Canada, the federal regulator, approved the first HPV vaccine on 10 July, 2006, for females 9 through 26 years of age. In February 2007, the National Advisory Committee on Immunization (NACI) published its recommendations on HPV vaccines taking into account the burden of disease and vaccine characteristics. NACI's recommendations are considered by F/P/T jurisdictions as they develop and implement their immunization programs.

A multidisciplinary joint CIC-NACI HPV Vaccine Expert Working Group was established in May 2006 to develop comprehensive recommendations for HPV vaccine programs using the analytical framework[(1)]. It included members from the CIC and NACI, as well as disease experts and representatives from the Cervical Cancer Prevention and Control Network, College of Family Physicians of Canada, Society of Obstetricians and Gynaecologists of Canada, Society of Gynecologic Oncologists of Canada, First Nations and Inuit Health Branch of Health Canada, and Biologics and Genetic Therapies Directorate of Health Canada. Broad representation from public health, vaccinology, sexual health, gynecology, cancer, aboriginal health, nursing and family medicine ensured that multiple perspectives were discussed and that the group's mandate was met. The resulting analysis and recommendations were forwarded to the CIC for consideration in the development of their recommendations on the HPV vaccine program and options.

This report summarizes the components of the analytical framework on HPV immunization programs and presents the recommendations for the implementation of a publicly funded HPV immunization program across the country, aiming for a harmonized approach towards the introduction of the vaccine in Canada. A worksheet table summarizing the responsibilities of NACI and CIC for the components of the analytical framework is included as Appendix 4.

Following the NACI recommendations, the Federal Budget 2007 provided $300 million to provinces and territories through a third-party trust fund to launch HPV vaccine programs. The HPV Vaccine Trust, distributed on a per capita basis, is intended to support the purchase of the HPV vaccine by the provinces and territories. The vaccine will be used in a publicly funded HPV immunization program for residents, including all First Nations and Inuit residents both on and off reserve, over 3 years. There is flexibility provided in the use of a trust mechanism such that provinces and territories can use this money as appropriate within their jurisdictions. The Government of Canada will work

with the P/Ts to facilitate access to the funding so that the vaccine is available equitably across Canada. The provinces and territories are responsible for the delivery of immunization programs and will consider their own set of circumstances in decisions about the implementation of HPV immunization programs.

2. Burden of disease

There are approximately 40 genotypes of HPV that affect the human anogenital area, including about 15 that are recognized as carcinogenic. Cervical cancer is the first type of cancer to have been associated with HPV: the virus is present in 99.7% of cervical cancer cases. HPV is also linked with a number of other cancer sites, in particular the anus, vulva, vagina, penis and oropharynx. Types 16 and 18 are present in 70% of cervical cancers in North America, and similar epidemiologic characteristics have been found in many other parts of the world.

The risk of acquiring an HPV infection occurs very shortly after the onset of sexual activity[2]. Approximately 20% of 15-year-old Canadians have had a sexual encounter. In North America, the lifetime cumulative incidence of HPV infection is estimated at more than 70% for all types together, which makes HPV the most common sexually transmitted infection. The highest prevalence is found in the 20-24 age range[2,3]. In a multi-year study of aboriginal women in Nunavik, northern Quebec, infections with any HPV type and high-risk HPV types were detected in 29.1% and 20.2% of women respectively. The most common HPV type was HPV-16; infections with HPV-16 and HPV-18 accounted for 23.8% of all HPV infections[4]. HPV prevalence in this population was found to be similar to that observed among female university students in Montreal[5,6] and health clinic attendees in Winnipeg and Nunavut[7,8].

Most HPV infections are asymptomatic and self-limiting, clearing within 24 months. However, persistent infections with oncogenic types may lead to cancer. This process typically takes a number of years or even decades. Without treatment, most invasive cancers are eventually fatal. Survival rates vary according to treatment and stage at the time of diagnosis.

The age-standardized cervical cancer incidence rate for Canada is estimated to be 7.3 cases per 100,000 for the year 2007, a marked decrease compared with the 1978 rate (14.7 per 100,000). However, in the last 10 years the rate of decline has been slower, the incidence in 1997 being 8.7 cases. At 1,350 new cases estimated for 2007 in Canada, cervical cancer is the 13th most common cancer among Canadian women of all ages but the third most common among those aged 20 to 44. Annually, there are approximately 390 deaths related to cervical cancer in Canada[9].

There are many avenues for cervical cancer prevention in Canada. Immunization is considered to be part of a primary prevention strategy and cervical cancer screening part of a secondary prevention method. Approximately 5,500,000 cervical cancer screening examinations (Pap tests) are performed each year. Despite this, not all women attend regularly for screening. The results of a meta-analysis indicated that 54% of patients with invasive cervical cancer had inadequate screening histories, and 41.5% had never been screened. An estimated 29.3% of failures to prevent invasive cervical cancer can be attributed to false-negative Pap smears and 11.9% to poor follow-up of abnormal results[10]. The psychosocial impacts of an abnormal screening result are significant, and the need for a repeat examination or for treatment creates anxiety and entails substantial inconvenience for women. Screening decreases the risk of progression of a precancerous lesion to cancer but has no role in preventing transmission.

Given that the disease burden involves not only cervical cancer but also cancer precursors detected by screening, the advantage of a primary prevention strategy with immunization is the expected reduction in the financial costs and psychological impact associated with the follow-up of abnormal Pap test results and the early treatment of cancer precursors. When implemented in a school-based

program, immunization is likely to reach some groups that may have lower cervical cancer screening rates or poor follow-up.

HPV is also linked with non-cancerous lesions, such as anogenital condylomas. This condition is associated with types 6 and 11 in 90% of cases. While there are no precise epidemiological data on its incidence in Canada, it is a relatively common condition. Recurrent respiratory papillomatosis, a much less common but potentially serious disease, is also associated with HPV.

More detailed information on the burden of HPV-associated diseases can be found in the NACI *Statement on Human Papillomavirus Vaccine*[2].

3. HPV vaccine characteristics

Two HPV vaccines have been tested in clinical studies: Gardasil™, by Merck Frosst, and Cervarix™, by GlaxoSmithKline. The quadrivalent vaccine Gardasil™, which contains HPV types 6, 11, 16 and 18, was authorized for sale in Canada for females between 9 and 26 years of age in 2006. The bivalent vaccine Cervarix™, which contains HPV types 16 and 18, has been submitted for approval. Cervarix™ includes a new adjuvant, AS04, which contains monophosphoryl lipid A, derived from bacterial cell walls and alum.

Gardasil™ and Cervarix™ are subunit vaccines containing virus-like particles produced by recombinant technology. The vaccines cannot cause disease because they contain no live biologicals or DNA and are not infectious. They have been shown to be safe and generally well tolerated[11-14]: in clinical trials, systemic adverse events such as headache or fatigue were reported by a similar proportion in the vaccine and placebo recipients[2].

In clinical trials, the vaccines showed a remarkable 90%-100% efficacy against the development of high-grade cervical lesions associated with HPV 16 and 18 for periods of up to 5.5 years.

Immunogenicity data are available for women aged 9-26 and boys aged 9-15 vaccinated with Gardasil™ and for women aged 10-45 vaccinated with Cervarix™[15-18]. One month following the administration of the third dose, nearly all participants (≥ 99%) had developed antibodies against the types of HPV contained in the vaccines. The antibody levels after vaccination have been found to be 10-100 times higher than the levels produced by natural infection. Comparative studies have shown that the average anti-HPV geometric mean titres (GMTs) in preadolescents and adolescents aged 9-14 were twice those in women aged 15-25[16]. One month after the second dose of Gardasil™, GMTs against all virus types included in the vaccine in youths aged 10-15 were higher than the GMTs observed 1 month after the third dose in women aged 16-23[16]. The vaccine was well tolerated in both age groups.

The seroconversion rate 1 month after the second dose exceeded 97.5% for all types of HPV included in the vaccine[16]. Robust anti-HPV GMTs were observed at this time.

Efficacy data are not available for the 9-13 age group since most are not sexually active and pelvic examinations are not performed and that CIN does not develop at such a young age. However, immunogenicity results showing high antibody response in young girls would support no inferiority in protection as compared with older age groups.

A recent double-blind, placebo-controlled study examined the extent of immune memory in response to a primary vaccination series with a quadrivalent HPV vaccine. Serum anti-HPV levels declined after vaccination but reached a plateau at month 24 and remained stable through month 60. Administration of a challenge dose of vaccine induced a classic anamnestic response, with anti-HPV levels 1 week post-challenge reaching levels observed 1 month after completion of the three-dose

primary series. At 1 month post-challenge, anti-HPV responses were higher than those observed 1 month after the third dose. The authors concluded that HPV vaccine induces high efficacy and stable anti-HPV levels for at least 5 years[19].

The main criteria used in clinical trials to establish the efficacy of the vaccines were as follows:

- a reduction in the number of moderate and severe abnormalities (CIN 2/3) and adenocarcinoma *in situ*; and
- a reduction in the incidence of persistent infections with the types of virus included in the vaccine[20].

Cervical cancer has not been used as the primary criterion for measuring the efficacy of HPV vaccines in clinical trials because of the time it takes for the disease to develop and the need for appropriate clinical management of premalignant lesions to be provided immediately[21].

Aside from the prevention of lesions caused by HPV 16 and 18, Cervarix™ has been shown to be 35% to 60% effective in preventing infections caused by types 31 and 45, which are responsible for 8%-10% of cervical cancers[15,22]. Cross-protection data on Gardasil™ are emerging. Gardasil™ has also been shown to provide 99% protection against anogenital condylomas in women.

There is no evidence that women who have already been infected with one of the types contained in a vaccine will be protected against that type by vaccination. This is why it is preferable to vaccinate girls before the onset of sexual activity. Currently, there are no data on the efficacy of the vaccines in men or on the interchangeability of the two HPV vaccines.

Manufacturers currently recommend a schedule of three doses administered at 0, 2 and 6 months for Gardasil™ or 0, 1 and 6 months for Cervarix™. A clinical trial was started in 2007 to determine the immunogenicity of a schedule of two doses of Gardasil™ spaced 6 months apart in girls aged 9-13 compared with three doses given to young women aged 16-26. The study, involving 825 girls, is funded by the ministries of health of British Columbia, Quebec and Nova Scotia[23]. A clinical trial is also planned to determine the immunogenicity of a two-dose schedule with Cervarix™.

HPV vaccines are safe and well tolerated. Clinical trials have found no increased number of serious adverse events in girls/women who received HPV vaccine compared with those who received placebo, and the types of serious adverse event reported were similar in the vaccine and placebo groups. There was no evidence that vaccination resulted in allergic reactions or other immune-mediated disease[2]. As of 30 June, 2007, 13 cases of possible Guillain-Barré syndrome (GBS) after vaccination with Gardasil™ had been reported in the United States with distribution of more than 7 million doses. Expert review indicated that only two out of the 13 met the case definition of GBS. These two cases occurred within 6 weeks of vaccination with Gardasil™ alone. Because GBS occurs at a rate of 1-2/100,000 person-years during the second decade of life, 13 reported cases of GBS are within the expected numbers[24].

Additional information on HPV vaccines can be found in the NACI *Statement on Human Papillomavirus Vaccine*[2].

4. Immunization strategies

Four options for publicly funded HPV immunization programs were considered initially for the disease modelling and the economic analysis. Under each option, estimations for coverage are included.

Option 1: One female cohort selected from grades 4 to 7 (aged 9-14)

(a) To immunize 80% of school-aged girls in either grade 4, 5, 6 or 7 with the required doses of the HPV vaccine within 2 years of program introduction.

(b) To immunize 90% of school-aged girls in either grade 4, 5, 6 or 7 with the required doses of the HPV vaccine within 5 years of program introduction.

Option 2: Two female cohorts from grades 4 to 12 (aged 9-18)

(a) To immunize 80% of two cohorts of school-aged girls between grades 4 and 12 with the required doses of the HPV vaccine within 2 years of program introduction.

(b) To immunize 90% of two cohorts of school-aged girls between grades 4 and 12 with the required doses of the HPV vaccine within 5 years of program introduction.

Option 3: School-based program, multiple female cohorts (at minimum one cohort from each elementary, junior and high school age group, i.e. a total of three cohorts)

(a) To immunize 80% of school-aged girls within the cohorts vaccinated, at least one cohort from each of elementary, junior and high school grades, with the required doses of the HPV vaccine within 2 years of program introduction.

(b) To immunize 90% of school-aged girls within the cohorts vaccinated, at least one cohort from each of elementary, junior and high school grades, with the required doses of the HPV vaccine within 5 years of program introduction.

Table 1 illustrates option 3, with immunization of grades 4, 7 and 12 females. It reflects the duration/number of years for which three cohorts, two cohorts and then only routine HPV immunization of one cohort would have to be continued.

Table 1 Duration/numbers of years of HPV program implementation

Year	**Grade 4 (5 or 6)** (HPV immunization program)	**Grade 7 (8 or 9)** (Catch-up)	**Grade 12** (Catch-up)
One	√	√	√
Two	√	√	√
Three	√	√	√
Four	√	–	√
Five	√	–	√
Six	√	–	–

Option 4: All females in the recommended range of 9-26 years (option 1 is included in this option; this is mostly a catch-up program)

(a) To immunize 80%* of women aged 9 through 16 with the required doses of HPV vaccine within 2 years of program introduction.

(b) To immunize 60% of women aged 17 through 26 with the required doses of HPV vaccine within 5 years of program introduction.

* Assumptions:
    - Catch-up of all school-aged females will take place in 2 years.
    - Opportunistic immunization of other cohorts aged 15-26 will occur outside school programs as these individuals visit a health care provider.

5. Cost-effectiveness of HPV immunization

While clinical studies are sufficient for vaccine licensure, they cannot provide information on the long-term epidemiologic and economic consequences of the vaccine. When data from long-term, follow-up clinical studies are not available, an alternative information source is mathematical models. Mathematical models have been developed to project the long-term benefits and costs of vaccination and to evaluate alternative HPV vaccination strategies. Two types of mathematical model have been used: Markov models (also referred to as cohort models) and transmission dynamic models. Markov models are probabilistic and linear: the progression of HPV disease is simulated for a single cohort over its expected lifetime, much as a cohort is tracked in a life-table analysis. Dynamic models are deterministic and nonlinear: individuals constantly enter the model as they are born and exit it as they die. A dynamic model does not track just a single cohort but, rather, the changing population over time. Dynamic modelling accounts for how HPV vaccination reduces the prevalence of infection in the population over time, assessing the impact of herd immunity[25]. However, fitting parameters into dynamic models is often more challenging than in Markov models because of high computing demands.

At this time, the direct costs of the immunization program are vaccine costs (three doses of quadrivalent HPV 6/11/16/18 vaccine and a booster shot if immunity to primary vaccination is not shown to be lifelong; $134.95/dose) and the cost of administering each dose (approximately $10 to $13/dose if administered by a nurse through a school-based program). A school-based vaccination program would entail few indirect costs, whereas the indirect costs associated with a physician-based program would include patient and/or parent time taken for three (or four if a booster dose is required) office visits. For Canada, the total program cost would include cost of vaccine, distribution of the vaccine, cold chain maintenance, education, obtaining informed consent and administration of the vaccine by public health nurses through a school-based program. This has been estimated by the British Columbia (BC) Centre for Disease Control at $9 to $10 million per cohort of school-aged girls in BC (approximately 30,000 girls/cohort).

The clinical trials published to date have shown a decrease in the incidence of HPV 16 and 18 infections, CIN 1 and 2/3, vaginal and vulvar cancers, and genital warts following HPV vaccination[26-28]. None of these studies examined the impact of vaccination on anal, penile, head and neck cancers or recurrent respiratory papillomatosis. The longest follow-up after vaccination in these clinical trials was 5.5 years[18]. Since the interval from HPV infection to cervical cancer is long in most cases (usually decades), to date none of these trials has reported invasive cervical squamous cell carcinoma, adenocarcinoma or mortality outcomes.

Since long-term efficacy data of the HPV vaccine are still lacking, mathematical models are used to project the impact of a HPV vaccine on HPV prevalence, CIN and cervical cancer incidence. Each of the published studies to date included various assumptions on vaccine coverage, efficacy and duration of protection in their models (Appendix 2).

5.1 International modelling studies

The published dynamic models, assuming either a 10-year or lifelong duration of vaccine immunity, predict approximately 95% reduction in HPV infections, 62% to 93% reduction in cervical cancer cases (if vaccinating girls only) and 64% to 91% reduction in cervical cancer cases if vaccinating girls and boys[29-34]. The studies using a Markov model found that the use of HPV vaccine in 12-year-old girls would reduce the incidence of HPV infections by approximately 13%, CIN 1 by 20% to 30% and CIN 2/3 by 46% to 66%. Kulasingam and Myers[35] and Sanders and Tairs[36] showed a reduction in cervical cancer cases of 15% and 20% respectively when the duration of protection is assumed to be 10 years, whereas other studies assuming lifelong duration of immunity show approximately 50% to 75% reduction[37-40].

Published cost-effectiveness studies have included direct medical costs, such as the cost of the vaccine, as well as the costs of managing and treating cancer precursors and cervical cancer (Appendix 2). None of these studies included the costs associated with some non-cervical cancers (vaginal, vulvar, anal and head/neck cancers). The dynamic models[30,32,34] showed a lower incremental cost-effectiveness ratio for the bivalent vaccine, which ranged from approximately $15,000 to $25,000 for a girls-only program. The use of a quadrivalent vaccine in girls only gives an incremental cost per quality adjusted life year (QALY*) varying from approximately $3000 to $37,000, depending on the model used, duration of immunity and other assumptions[34,40]. A universal immunization program for girls aged 14 and under would cost an estimated $15,000 to $31,000 per QALY if the vaccine were effective for life and approximately $400 per person vaccinated. This threshold could be considered acceptable for a health intervention. Cost per QALY increases progressively after the age of 14, as does the proportion of girls infected with one of the types contained in the vaccine. The studies using a Markov model[35,36,38,40] produced similar results to the dynamic models, showing an incremental cost per life year gained ranging from approximately $32,000 to $93,000 when bivalent HPV vaccine was introduced for 12-year-old girls, as compared with the current screening programs; the cost per QALY in these studies ranged from $23,000 to $31,000.

Introduction of the HPV vaccine for girls and boys was estimated at an incremental cost of approximately $170,000[34] to $440,000[30] per QALY.

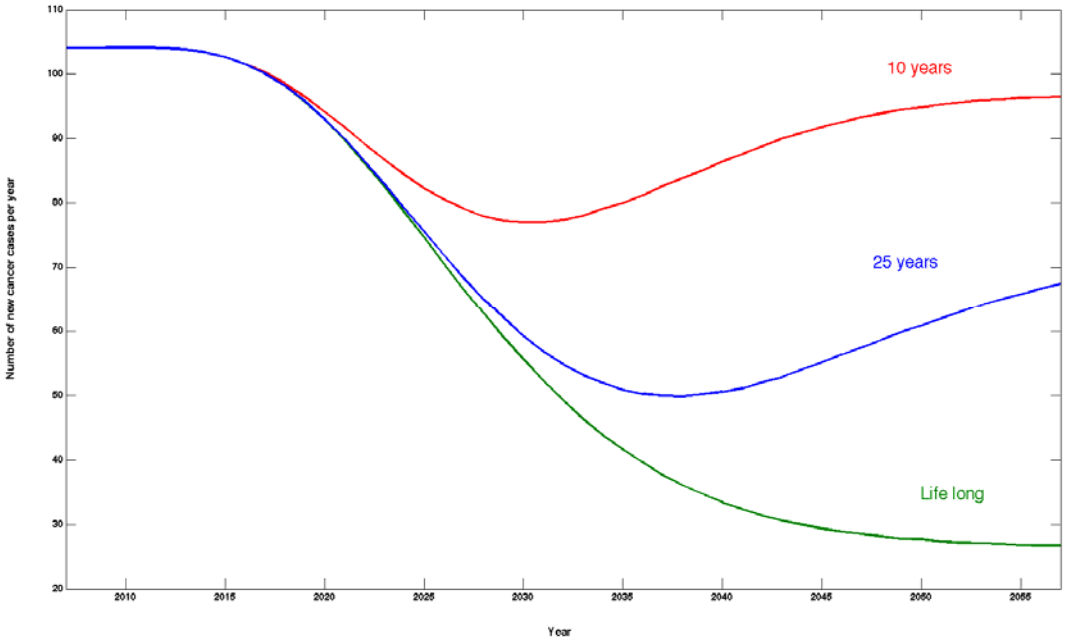
Published mathematical models have shown that the cost-effectiveness of HPV vaccination is highly sensitive to the duration of vaccine protection. However, varying vaccine coverage from 70% to 100% has little impact on the cost-effectiveness predictions.

5.2 Canadian modelling studies

Pourbohloul and Günther[42] have developed a transmission dynamic model and performed an extensive sensitivity analysis to predict HPV 16/18-associated disease prevalence and incidence in British Columbia. The transmission dynamic model assesses the epidemiologic consequences of alternative strategies for immunization with HPV vaccines in British Columbia, as well as in Canada.
Figure 1 shows the expected number of new cervical cancer cases using different vaccine parameters (10 years, 25 years or lifelong immunity) for vaccination of 14-year-old females, based on data from British Columbia.

*QALY takes into account both the quantity and the quality of life generated by health care interventions. It is the arithmetic product of life expectancy and a measure of the quality of the remaining life years. QALYs provide a common currency to assess the extent of the benefits gained from a variety of health interventions. When combined with the costs of providing the interventions, cost-utility ratios result; these indicate the additional costs required to generate a year of perfect health (one QALY)[41].

Figure 1 **Incidence of cervical cancer following immunization of 14-year-old females, assuming 10 years, 25 years or lifelong duration of vaccine immunity**

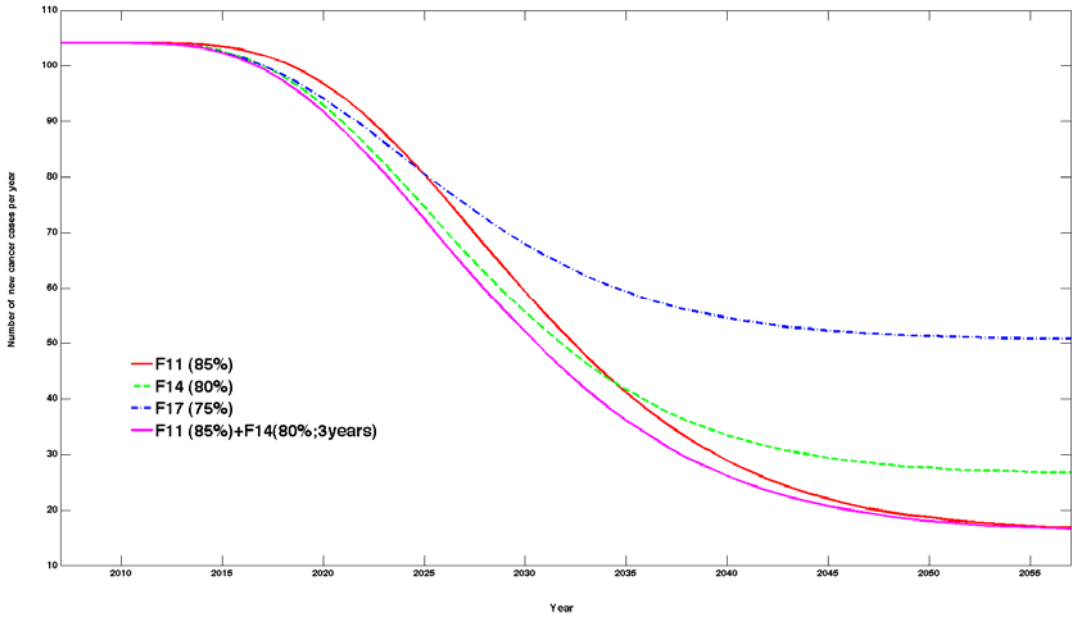


For each program strategy, the impact of vaccinating girls only versus boys and girls had a modest impact on the estimated number of new cervical cancer cases, especially when considering that twice as many vaccines would be needed for the latter strategy.

With the assumption of lifelong vaccine protection, all strategies caused the annual cancer incidence to drop significantly over 50 years after the initial delay (due to the long time lag between HPV infection and development of full-blown cervical cancer). It was further shown that the reduction in cancer incidence after 50 years was largest when the vaccine was administered at a young age and smallest when administered at an older age. With lifelong protection, vaccine immunity will not wane; therefore, vaccination of girls at an age as young as possible results in the best performance, especially when combined with a 3-year catch-up program for 14-year-old girls. On the other hand, the results for an assumed vaccine protection of 10 years were qualitatively different (Figure 1). Even though the annual cancer incidence dropped for all strategies after an initial delay, the reduction was significantly smaller compared with the assumption of lifelong vaccine protection, and a rebound was observed around the year 2030.

Figure 2 illustrates the projected number of new cervical cancer cases per year if vaccinating girls only at different ages (11, 14 or 17 years old) assuming lifelong vaccine immunity.

Figure 2 Projected cancer incidence after various HPV vaccination strategies[42]



The model* has been used to assess the cost-effectiveness ratio in terms of CDN$ per QALY of three school-based strategies: (1) a girls-only program at age 11 (F11); (2) a girls-only program at age 14 (F14); (3) a combined F11 and F14 program for girls only for 3 years followed by an F11 program. Compared with the screening program, all three strategies were similarly cost-effective, at $24,530/QALY with vaccination of 14-year-old girls, $24,945/QALY with vaccination of 11-year-old girls and $25,417/QALY with the combined program[34].

Similar results were obtained with the compartmental deterministic model developed by Brisson and collaborators[40,43]. Among 12-year-old girls, these authors estimated that the number needing to be vaccinated to prevent an episode of genital warts would be 8 and to prevent a case of cervical cancer would be 324[43]. For Canada, this model estimated that vaccination of 12-year-old girls would result in a decrease of 62% in cervical cancer cases at a cost of $20,512 to $31,060 per QALY[40]. Similar estimates were obtained by the compartmental deterministic model and the transmission dynamic model as to the impact of the duration of vaccine protection on disease incidence.

6. Acceptability of HPV immunization

6.1 International studies

Most published studies emphasize the public's low level of knowledge about HPV, especially its prevalence and links to cervical cancer[44-52]. Despite this lack of knowledge, there is significant public interest in HPV vaccines. The intention to be vaccinated against HPV is common among female adolescents and young women[49,50,53-61], as well as among parents for their young adolescents[45,46,52-55,61-65].

*Assumptions: 100% vaccine efficacy, 85% and 80% vaccine uptake for the 11 and 14-year-olds respectively, lifelong duration of immunity, vaccine cost of $135.95 and administration cost $12.66 per dose, and cost of Pap and cytology $74.

Several factors influence attitudes about HPV vaccination. The most salient issues are vaccine efficacy and safety; perceived risk and severity of the disease; recommendation by a physician; and, for health care providers, professional society recommendation. Health care providers are the most likely people to influence parental decisions regarding vaccination. They are also the main source of information on HPV vaccination for the public.

6.2 Canadian studies

In a national study to determine parental intention to vaccinate their daughters with the HPV vaccine, parents of children aged 8 to 18 were recruited from across Canada between June 2006 and March 2007 through random digit dialing[66]. Participants were asked to respond to a series of questions in the context of a grade 6 (age 11-12 years), publicly funded, school-based HPV vaccine program, including their intention to have their daughter vaccinated with the HPV vaccine. Parents were also asked about a series of characteristics known to predict intention to vaccinate, including attitudes towards vaccination, perceptions about the role of the HPV vaccine in influencing sexual behaviour, social norms, up take of childhood vaccines, knowledge of HPV and cervical cancer, as well as demographic characteristics. Backwards logistic regression was conducted to calculate adjusted odds ratios (OR) in order to identify the factors that predict parents' intention to have their daughter(s) vaccinated against HPV.

Of the 1,350 respondents, over 70% (73.8%, 95% confidence interval [CI]: 71.9%-75.7%) reported that they intended their daughter to be vaccinated against HPV. Across the country, in crude analysis, intention to vaccinate in different regions of residence ranged from 62.8% (95% CI 60.2%-65.4%) in British Columbia to a high of 82.6% (95% CI 80.6%-84.6%) in Atlantic Canada ($p < 0.01$). In multivariable modeling, parents who had positive attitudes towards vaccines (OR = 9.9, 95% CI: 4.7-21.1), parents who were influenced by subjective norms* (OR = 9.2, 95% CI: 6.6-12.9), parents who felt that the vaccine had limited influence on sexual behaviour (OR = 3.2, 95% CI: 2.2-4.6) and parents who thought that someone they knew was likely to get cervical cancer (OR = 1.5, 95% CI: 1.1-2.1) were more likely to intend to have their daughters vaccinated with the HPV vaccine. Parents who were older compared with those who were younger (OR = 0.6, 95% CI: 0.5-0.8) and parents who resided in British Columbia compared with Atlantic Canada (OR = 0.5, 95% CI: 0.3-0.9) were less likely to do so.

The most important predictor of parental intention to vaccinate was the psychological construct assessing parental attitudes towards vaccines in general and the HPV vaccine in particular. This construct examined aspects such as HPV vaccine safety and efficacy along with overall attitudes towards vaccines. Recommendations to vaccinate from health professionals, family and friends, and community leaders, with physicians in particular, were also important predictors of parental intention to vaccinate with the HPV vaccine. In this study, cultural background, religious beliefs, specific religious affiliations and educational background were not predictors of parents' intention to have their daughters vaccinated.

Between May and November 2006, an anonymous, self-administered questionnaire was mailed to all obstetricians/gynecologists and pediatricians and to a random sample of family physicians in British Columbia, Quebec and Nova Scotia (1,268 respondents, response rate of 50.2%)[68]. Overall, 28% of physicians scored ≥ 6 on 9 knowledge questions. The mean score of obstetricians/gynecologists (5.6) was higher than that of family physicians (3.8) or pediatricians (3.2). However, most intended to recommend the HPV vaccine; 95% felt that the vaccine should be given before the onset of sexual activity; and 80% felt that the best age for vaccination was < 14

*Subjective norm component represents a person's beliefs about whether relevant others think he or she should perform the behaviour and his or her motivation to comply with those others[67].

years. Overall, 88% of Canadian physicians surveyed intend to recommend the vaccine if it was publicly funded and 84% if patients had to pay for it.

7. Feasibility of eventual HPV immunization

HPV vaccines are designed to prevent infection with HPV genotypes included in the vaccines but are not designed to treat women who have already been infected with these genotypes. Indeed, HPV vaccination would best be administered before the onset of sexual activity[2].

Table 2 illustrates some results of a Canadian study on adolescents' sexual health.

Table 2 Sexual behaviours of Canadian adolescents by age group[69]

	14 years old	15 years old	16 years old	17 years old
Canadian teens reporting being sexually active	7%	20%	34%	45%

In addition, according to the Canadian Community Health Survey 3.1 (2005), 61.3% of respondents between the ages of 15 and 24 and 27.9% of respondents between the ages of 15 and 17 reported that they had sexual intercourse.

School-based vaccination programs remain an effective way to reach young girls and to make sure that all vaccine doses are administered. In 1998-1999, 97.1% of Canadians between 7 and 14 years of age were enrolled full-time in school[70]. Published data suggest that immunization coverage with existing programs is high when school-based programs are used and higher in primary school than high school[71].

However, if a booster dose is needed, it may be difficult to reach vaccinated women because they will not be in the school system any more. The accessibility of young adults to vaccination services may also be problematic. Currently in Canada, as in many other developed countries[72,73], there are no special immunization services for adults outside travel clinics and influenza vaccination.

Finally, although this aspect has not been well studied, some difficulties may emerge when implementing a sex-based (girls only) vaccination program.

8. Ability to evaluate immunization programs

The evaluation of HPV immunization programs over time is extremely important, given the need to evaluate impact over the long term and, as with many other vaccine programs, the unknown duration of protection at the start of implementation. Monitoring and evaluating HPV immunization programs will require standardized HPV testing methods, standardized units of measurement for HPV antibodies, population-based reporting systems for HPV-associated diseases, and registries or information systems for follow-up of vaccine coverage[21,74]. Effective linkage between the latter databases will also be important. Regular studies of the knowledge, attitudes and practices of the public and health professionals will also be necessary.

At a national level, much effort is still required to prepare for the evaluation of new HPV immunization programs, and few data are available in the literature (Appendix 3 presents the literature review). Infection with HPV is not reportable in any province or territory of Canada, so it is difficult to know the prevalence, incidence or distribution of HPV genotypes in the population[75]. As for all immunization programs, provincial and national authorities will require a detailed

evaluation plan for HPV vaccination programs. Significant investments have to be made to conduct surveillance and program evaluation over the long term, and a multidisciplinary approach is needed.

8.1 Availability of systems to measure coverage and vaccine utilization, and quality of vaccination services

As with other health care programs, immunization is primarily a provincial and territorial responsibility. The Canadian Immunization Registry Network (CIRN) and the F/P/T working group of the CIC have been working together for the past 6 years to develop a national network of immunization registries across the country. CIRN has developed the standards and guidelines for a commonly used methodology to measure coverage routinely using registry data. Currently, five provinces have fully functional registries, and the remaining jurisdictions are either planning or evaluating the immunization module contained in INFOWAY's PANORAMA public health surveillance system. In the meantime, there are several options for measuring coverage. The Adult and Childhood National Immunization Coverage Survey, conducted every 2 years, provides national estimates for 17-year-olds in the childhood survey and for the adult population. However, the concern with these studies is that they are not able to assess subpopulations and that non-participation bias cannot be excluded. Another alternative is to use provinces with established immunization and cancer screening registries as special pilot sites. This approach would enable a more comprehensive assessment of vaccination coverage, but data extrapolation to other provinces and territories may not be appropriate.

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

8.2 Availability of systems to measure impact of HPV-related infections

It is imperative to establish an HPV type distribution baseline that is representative of different populations across Canada and to follow this up with a long-term surveillance program to monitor the impact of HPV vaccination against types 16 and 18 (6 and 11) on the overall incidence and prevalence of HPV infections. Ultimately, this surveillance system may reflect shifts in HPV type distribution as a result of vaccination against types 16 and 18 (6 and 11), such as an increase in types not included in the vaccine.

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

Although cervical cancer is the most important long-term health outcome, other endpoints are needed to monitor the short- and mid-term impact of vaccination on HPV-related infections. Malignancies develop slowly, and although cancer registries are available they will be useful only years after the implementation of HPV immunization programs. Endpoints used in clinical studies could be used as short- and mid-term evaluation outcomes. A consensus report from a World Health Organization expert group proposed histologically confirmed high-grade CIN or worse (including cervical cancer) as an acceptable surrogate endpoint[20,21,72]. Monitoring of cervical lesions will

require development of population-based reporting systems for HPV-associated infections[74]. Type-specific persistence of infection (the presence of the same HPV type at two or more consecutive visits separated by 6-12 months) could also be an outcome measure[21]. However, commercial tests for HPV testing and typing are not yet routinely available in the Canadian public health system.

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

In Canada, the public health burden of condylomas is not known, nor are there registries to measure their incidence or prevalence. Studies are needed to evaluate the prevalence and incidence of this disease.

Indeed, measuring the impact of the immunization program on HPV-associated diseases and on screening practices will require important efforts. A baseline assessment of HPV-associated diseases (including those caused by types not covered by the vaccine), of screening practices and of costs could be useful during the implementation of vaccination programs[74]. To detect a possible replacement in circulating HPV types, a surveillance system should be developed.

8.3 Availability of systems for linking health outcomes databases, immunization registries and population registries

Even without national/provincial electronic immunization registries, it will be essential to be able to contact HPV-vaccinated women if an additional dose of the vaccine is needed. Relying on mass media and communication to professionals to disseminate information about the need for a booster dose would be less effective than individualized notification. Specific modalities to inform health authorities about HPV vaccine status will have to be organized before HPV program implementation.

Canada Health Infoway supports the development of the Pan-Canadian Electronic Health Record, as well as the standardization of laboratory data (to ensure that data can be exchanged among systems), including cytopathology data.

The immunization management module of the future PANORAMA public health information system could provide data on the HPV vaccination status of residents in each Canadian jurisdiction if the vaccine is provided by public health providers or if the information about the vaccination is reported by private providers to public health authorities.

In the meantime, it may be possible to link existing regional/provincial databases (immunization and cancer) for evaluation. Also, national immunization rates can be measured using the Adult and Childhood National Immunization Coverage Survey or by aggregating coverage estimates from the jurisdictions once the national coverage standards are adopted[76]. The possibility of restricting certain aspects of the evaluation to predetermined geographic areas could be explored. Additional data from these areas could facilitate future decision-making on the prevention of HPV infections and related anomalies.

To conclude, evaluation of the HPV vaccination program will be crucial and complex. Evaluation requires the development of a comprehensive plan and will demand significant resources.

9. Research questions

Many questions raised at the National HPV Research Priorities Workshop in Quebec City in November 2005 remain pertinent and unanswered[75]. While it is important to avoid delays in offering HPV vaccine on a routine basis, it is also important that research gaps are answered. Similar research priorities were identified by NACI in its HPV statement of February 2007[2].

9.1 Fundamental research

Baseline data are needed on the transmission of HPV in subpopulations (e.g. Aboriginal, immunocompromised), the distribution of HPV types and the prevalence, duration, natural history and costs (in terms of screening, diagnosis and treatment) of HPV-associated diseases. It would be useful to know the impact of migration, ethnicity, underlying health status and geographic isolation on the effectiveness of primary and secondary prevention programs, and the psychosocial burden of identified precursors of disease on particular groups.

9.2 Intervention research

Alternative HPV immunization schedules need to be examined. Given the observation during clinical trials that younger girls produced a high antibody response to HPV vaccine after two doses, there are research studies under way to examine a two-dose immunization schedule. A clinical trial in which two doses of vaccine are being administered to girls aged 9-14 began in 2007 in four Canadian provinces. Data on the short- and long-term immunogenicity, efficacy and effectiveness associated with a two-dose as compared with a three-dose schedule will be available within the next few years.

The possibility of administering HPV vaccine through an extended schedule could also be examined. One option is as follows: first two doses administered 6 months apart in primary school and the third dose in high school, if needed. The arguments underlying this proposal may be grouped into two categories, immunologic and operational.

(a) Immunologic arguments

- It is well known that spacing out doses generally produces higher antibody levels. This has been well demonstrated by the recombinant hepatitis B vaccine[77]. Further, there is no well-articulated justification for the schedules of 0, 1 and 6 or 0, 2 and 6 months proposed by the manufacturers.
- The administration of a catch-up dose after 5 years produces very high GMTs, much higher than those produced after primary vaccination. This has been observed for hepatitis B vaccines (Quebec cohorts)[78,79] and HPV vaccines[19]. In the context of HPV, with the goal of maximum protection before the onset of sexual activity, the administration of this dose in high school appears well justified on the basis of current knowledge. The lack of data on the duration of protection conferred by HPV vaccines adds further justification, as this schedule will produce the highest possible levels during the last in-school vaccination.

(b) Operational arguments

- Vaccination in primary school produces very high vaccination coverage at a relatively low administration cost. This is the best time to administer the vaccine, because of the quality of the immune response and the efficiency of administering the vaccine with other school-based programs. Some provinces already have a two-dose program for hepatitis B vaccination. The introduction in the near future of a two-dose schedule for hepatitis A and B using a combined vaccine is being considered by some jurisdictions. The combined hepatitis A and B vaccine and the HPV vaccine could be administered simultaneously, with no need to add a third vaccination session.

- If a third dose is needed in high school, it could be co-administered with Tdap (tetanus, diphtheria and pertussis), which would decrease related costs and increase vaccination coverage.
- The administration of two doses in primary school instead of three will probably increase acceptance by students, parents and health personnel while reducing costs and allowing for the vaccination of more young girls with the same resources.
- This schedule follows the approved schedule and does not constitute a contravention of existing norms regarding vaccination schedules. The principle of not repeating a vaccination course or doses when there have been extended intervals between doses is accepted in vaccinology.

Additional research is required on the consequences for safety and immunogenicity of co-administration with other vaccines and on the safety and immunogenicity of the vaccine during pregnancy, among immunocompromised individuals and in Aboriginal populations. The herd immunity according to level of coverage and the effect of natural infection on the antibody level in vaccinated individuals should be documented. Comparison of the use and effectiveness of bivalent versus quadrivalent vaccines should be undertaken. Other areas of priority are the impact of HPV immunization programs on cervical screening, in terms not only of compliance and screening intervals but also the sensitivity, specificity and predictive value of different tests.

9.3 Program delivery research

The potential effect of an immunization program on sexual behaviour, cervical screening programs and health care services needs to be investigated. Periodic measurement of knowledge, attitudes and beliefs of health professionals and the public regarding HPV immunization is a research priority. Creative means for increasing the accessibility of HPV vaccine for women should be developed. Finally, because of the risks, the burden of disease and the impacts of HPV infection may be different in subpopulations, such as immigrant and Aboriginal population, research is required to ensure that routine HPV immunization programs adequately meet the needs of those subpopulations.

10. Equity, ethical and other considerations

10.1 Equity

If the costs of the vaccine and its administration are to be paid by individuals themselves and not publicly funded, access to HPV vaccination will be problematic. In the past, when vaccines were not publicly funded, there was inequity of access. In Canada, social disparities exist in the utilization of cervical cancer screening[80], and cervical cancer affects mainly women of lower socio-economic status[81]. The absence of a publicly funded HPV immunization program would introduce an inequity in HPV and cancer prevention. A school-based immunization program could reduce these disparities by inclusion of all girls who go to school, without regard to their socio-economic characteristics. However, if no catch-up is implemented, such a program would remain inequitable for the teenagers outside the targeted school groups and for the women from 15 to 26 years old who are not going to school but for whom HPV vaccine is recommended.

Although the vaccine is not currently recommended for men, they could be equally concerned about HPV and the possible effects of the virus on their health. If future clinical studies demonstrate the efficiency of HPV vaccines for men and the vaccine is authorized for sale in men, ethical and equity issues will have to be re-examined.

10.2 Ethical considerations

Because it is a sexually transmitted disease, HPV infection is different from many other vaccine preventable diseases, such as mumps, measles, rubella or varicella. This difference could create

ethical dilemmas, many of them originating in the concern about sending a morally wrong message, such as endorsement of sexual promiscuity. Vaccination against hepatitis B, a virus that can also be transmitted through sexual contact, is now part of the publicly funded immunization programs offered in all provinces and territories[82]. Even if similar concerns were raised, implementation of hepatitis B immunization programs has not prompted major parental opposition in Canada. In a review of relevant studies, only between 6% and 12% of parents were concerned about the impact of HPV vaccination on the sexual activity of their child[54, 62, 65, 83]. Furthermore, safe sex and abstinence messages are not inconsistent with HPV vaccination. Finally, HPV vaccination will be voluntary in Canada; its use should not be compulsory and not lead to school-based requirements.

10.3 Other considerations

HPV vaccines are licensed in more than 60 countries[84]. Routine immunization programs have been implemented in a number of industrialized countries, including the United States, Australia and western European countries.

Canadian recommendations to implement a routine HPV program for girls ranging from 9 to 14 years of age, with catch-up programs where feasible, are in line with program recommendations from other countries. In general, routine programs primarily target females prior to adolescence and age of onset of sexual activity. Several countries in which HPV programs have been implemented have chosen a narrower age range than Canada for their routine immunization programs, including girls aged 11 and 12 years in the United States, girls aged 14 in France, girls aged 12 and 13 in Australia and girls aged 12 in Italy (Table 3). Catch-up programs have also been recommended in all of these countries to capture older females up to 26 years of age. Austria differs from most countries in that HPV is recommended for both boys and girls 9 to 15 years of age.

Table 3 Recommendations on HPV immunization programs outside of Canada

Country	Routine program recommended age group	Catch-up program	Reference – Web site accessed 16 November, 2007
Canada	One cohort, girls 9-14	n/a	
U.S.	Girls 11-12	13-26	http://wwww.cdc.gov/immwr/preview/immwrrhtml/rr5602a1.htm)
Australia	Girls 12-13	13-18	http://www.health.gov.au/internet/wcms/publishing.nsf/content/pbac-psd-gardasil-nov0
U.K.	Girls 12-13	14-17	http://www.google.ca/search?hl=en&q=HPV+recommendations+England&meta=)
France	Girls 14	15-23	http://www.reuters.com/article/health-SP/idUSL1174470620070711
Italy	Girls 12	n/a	http://www.medicalnewstoday.com/articles/71172.php
Belgium	Girls 10-13	14-15	http://www.medicalnewstoday.com/articles/71172.php
Norway	Girls 12	13-16	http://www.medicalnewstoday.com/articles/71172.php
Luxembourg	Girls 12	13-17	http://www.medicalnewstoday.com/articles/71172.php
Austria	Girls and boys 9-15	n/a	http://www.medicalnewstoday.com/articles/71172.php
Germany	Girls 12-17	n/a	http://www.medicalnewstoday.com/articles/71172.php

There is currently willingness within P/Ts to implement an HPV immunization program in Canada. However, ethical and other issues may vary depending on the immunization strategies chosen.

11. CIC recommendations

These recommendations represent the first statement by the CIC on the use of quadrivalent HPV vaccine, licensed in Canada in July 2006. They are based on the epidemiology of HPV, the HPV vaccine characteristics, the Canadian disease modeling and economic analysis, as well as on the feasibility and acceptability of HPV immunization programs. Currently, there are no precise epidemiologic data on the general incidence of anogenital condylomas; there are also no data on the effectiveness of HPV vaccines in males. Therefore, the HPV immunization program is recommended for women for cervical cancer prevention only at this time. As more knowledge about the vaccine becomes available, the recommendations can be revised accordingly. A table summarizing the recommendations is included as Appendix 5.

11.1 Goals

To decrease the morbidity and mortality of cervical cancer, its precursors and other HPV-related cancers in women in Canada through combined primary prevention (immunization) and secondary prevention (screening) programs.

11.2 CIC-NACI Working Group recommendations on disease incidence reduction

1. To reduce by 60%* the CIN 2/3 caused by HPV 16/18 in Canada within 20 years of introduction of an HPV vaccination program**.
2. To reduce by 60%* the incidence of cervical cancers (and other HPV-related cancers) caused by HPV 16/18 in Canada within 30 years of introduction of an HPV vaccination program**.

* These recommendations are based on the following assumptions:

- Vaccine efficacy is at least 95%, coverage at least 85% for 11-year-old girls, 80% for 14-year-old girls and 75% for 17-year-old girls.
- Duration of vaccine immunity is life-long.

** Immunization does not replace the need for fully implemented, organized, cervical cancer screening programs.

3. To reduce by 60% mortality due to cervical cancer caused by HPV 16/18 in Canada within 35 years of introduction of an HPV vaccination program***.

*** This recommendation is based on the following assumptions:

- There is a lag time between the diagnosis of cervical cancer and the time of death as an outcome.
- In general, the outcome of therapeutic measures (surgery, chemotherapy, radiation) for cervical cancer is known by 5 years past the time of diagnosis[85].

11.3 CIC-NACI Working Group recommendations on HPV immunization strategies and programs

A number of models have been developed to predict the long-term impact of various immunization strategies and estimate their cost-benefit ratio (see Appendix 4 for a review of pharmaco-economic evidence supporting the CIC-NACI recommendations). Vaccines are expected to prevent from 15% to 93% of cervical cancer cases, 46% to 66% of high-grade lesions and 20% to 30% of low-grade

lesions. The duration of protection has the greatest influence on the impact of vaccination. Much of the potential benefit could be lost if the vaccine's effectiveness lessens over time and thereby merely delays the development of cancer. Consequently, specific evaluation procedures should be put in place to measure the persistence of effectiveness, and strategies should be developed for reaching vaccinated women for booster doses if required.

Principles underlying the recommendations:

- HPV vaccines are highly immunogenic and produce antibody levels much higher than those conferred by natural infection[13,15].
- The vaccines are beneficial for all young women aged 9-26 years. However, because of their high cost, they must be used with optimal efficiency that is, maximizing the benefits of the resources consumed.
- For maximum vaccine effectiveness, it is preferable to administer HPV vaccines before the onset of sexual activity.
- The immune response in youth aged 9-11 is particularly good, reaching higher levels after two doses than those observed in young women aged 16-26 in whom the clinical efficacy of the vaccine was demonstrated[16] .
- It is preferable to administer vaccines in primary school in order to obtain higher vaccination coverage at a lower cost.
- Cost per QALY increases progressively after the age of 14.
- When possible, HPV vaccine can be co-administered with other vaccines (hepatitis B, Tdap) in existing school-based programs.
- Cervical screening will need to be continued after the introduction of the HPV vaccine since the vaccine will protect against certain types of HPV only, and more data on the length of protection and effect of vaccination are needed.

Because of the high prevalence of HPV infection, a routine immunization strategy is preferred over strategies targeting high-risk groups; such strategies are not efficient for HPV immunization and may also be viewed as unethical.

11.3.1 Routine immunization

To decrease the morbidity and mortality associated with cervical cancer, its precursors and other HPV-related cancers in women in Canada, CIC recommends school-based HPV vaccination of one female cohort to be implemented in all Canadian provinces and territories (option 1):

a) To immunize 80% of school-aged girls in either grade 4, 5, 6, 7 or 8 with the required doses of the HPV vaccine within 2 years of program introduction.

b) To immunize 90% of school-aged girls in either grade 4, 5, 6, 7 or 8 with the required doses of the HPV vaccine within 5 years of program introduction.

Particular efforts should be undertaken to achieve high vaccine coverage for routine programs in hard-to-reach and high-risk populations. Catch-up strategies could be extended to these populations.

Although the initial programmatic options examined were for schoolgirls in grades 4, 5, 6 or 7, the Canadian disease modeling and economic analysis indicated that vaccinating the grade 8 schoolgirl cohort is also a cost-effective strategy. Therefore, the grade 8 schoolgirl cohort has been included in the recommendation on routine immunization. When deciding on their routine programs, jurisdictions should consider their own population characteristics, such as the age at sexual debut and the ability to reach girls at different ages to achieve maximum vaccine coverage.

11.3.2 Catch-up immunization

For jurisdictions that wish to consider catch-up programs, these are options for consideration. The following table reflects the pros and cons of various catch-up options compared with a routine program for one school grade alone.

Table 4 Pros and cons of different publicly funded HPV catch-up immunization programs compared with a routine program for one school grade

Criterion	Routine program (no catch-up)	Option 1 Routine program + one additional female cohort	Option 2 Routine program + two additional female cohorts	Option 3 All females 9-26
Impact*	Delayed impact on HPV disease incidence and prevalence At mid-term, lowest impact when compared with other options	Delayed impact on HPV disease incidence and prevalence At mid-term, minimal impact when compared with other options	At short term, low impact on HPV disease incidence and prevalence At mid-term medium impact when compared with other options	Quick impact expected on HPV disease incidence and prevalence Highest impact when compared with other options
Cost-effectiveness	Best cost-effectiveness ratio when compared with other catch-up options	Good cost-effectiveness ratio when compared with other catch-up options	Cost-effectiveness will depend on age groups chosen	The worst cost-effectiveness ratio when compared with other catch-up options; the highest number "need to treat" for one case prevented
Feasibility	Best feasibility when compared with other options, especially if partially piggy-backed on existing vaccination programs	Good feasibility when compared with other options, especially if partially piggy-backed on existing vaccination programs	Feasibility will depend on age groups chosen	The lowest feasibility when compared with other options, especially for young adults and teenagers outside school; difficult to obtain high vaccine coverage
Accessibility	Best accessibility when compared with other options	Good accessibility	Good accessibility	Low to very low accessibility of some age groups
Equity	Less equitable than other options	Equitable for schoolgirls, inequitable for girls outside school	Equitable for schoolgirls, inequitable for girls outside school	Most equitable when compared with other options

*For all options, the duration of protection will determine the impact on HPV disease incidence and prevalence.

For all strategies, education and awareness campaigns for the population as well as professional education will be needed. However, at the present time, it is not feasible to implement option 3 in Canada.

11.3.3 Immunization schedules

Following the manufacturers' indications for the quadrivalent HPV vaccine, NACI recommends a three-dose schedule (0, 2 and 6 months)[2]. Currently, there are research studies under way to assess other HPV immunization schedules. As more information becomes available, Canadian provinces and territories may consider different schedules (e.g. extended schedules, two-dose schedules).

11.3.4 Impact of vaccination on cervical cancer screening

Cervical screening is an essential tool for evaluating the immunization program. While it is not within the CIC's mandate to issue recommendations on cervical cancer screening, the introduction of vaccination is expected to have a major impact ultimately on screening recommendations, and the two activities must now be planned simultaneously. An immunization program should constitute part of a comprehensive cervical cancer prevention program. In addition to determining the impact of vaccines on cancer screening any impact on sexual behaviour should also be evaluated.

Impact of HPV vaccination on screening outcomes: A lower prevalence of cervical lesions will result in a lower positive predictive value of cytology testing. HPV vaccination could also have an impact on the use of new screening tests (e.g. tests to detect the viral DNA of various HPV genotypes). Finally, vaccination will reduce the colposcopy rate by reducing the risk of precancerous lesions[25,26,86].

CIC recommends the development of a surveillance system to detect a possible replacement in circulating HPV types.

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

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

11.4 CIC/NACI Working Group recommendations on program evaluation

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

In parallel with implementation of an HPV immunization program, CIC recommends developing a detailed evaluation plan. Vaccination coverage, and the incidence and prevalence of HPV-associated diseases and cervical cancer will have to be monitored. The efficacy and duration of the protection

conferred by the vaccine as well as the psychosocial impact of vaccination (for instance, screening adherence in vaccinated women or the knowledge, attitudes and practices of the public and health professionals) will need evaluation.

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

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

APPENDIX 1

Worksheet – using the Analytical Framework

List of criteria in the Analytical Framework	HPV vaccine	Responsibility
Disease characteristics and burden	Not Important 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ Very Important	NACI
Vaccine characteristics	Not Important 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ Very Important	NACI
Alternative immunization strategies	Not Important 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ Very Important	NACI / CIC
Social and economic costs and benefits	Not Important 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ Very Important	CIC
Feasibility and acceptability	Not Important 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ Very Important	CIC
Ability to evaluate programs	Not Important 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ Very Important	CIC
Research questions	Not Important 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ Very Important	NACI/CIC
Other considerations	Not Important 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ Very Important	CIC (includes equity, ethical, legal, conformity of program, and others)
Overall, this vaccine should be publicly funded	Not Important 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ Very Important	CIC
Comparisons across vaccine types – ranking	Not Important 1 ☐ 2 ☐ 3 ☐ Very Important	CIC
Final vaccine recommendations		NACI
Final program recommendations		CIC

Disease Characteristics and Burden

- Nature and characteristics of the infective agents
- Clinical manifestations and complications
- Epidemiology of the disease
- Specific populations affected and risk factors
- Current disease treatment and preventability
- Social impact of the disease
- Economic impact of the disease

Vaccine Characteristics

- Nature and characteristics of immunizing agent
- Characteristics of commercial products
- Storage, handling, product format
- Vaccine manufacturers, production capacity and supply
- Administration schedule, number of doses, combination with other vaccines
- Nature and characteristics of the immune response
- Immunogenicity in different population groups
- Short- and long-term direct and indirect protection
- Impact on reduction of burden of disease
- Safety: rates and severity of adverse effects, contra-indications, precautions
- Potential interaction with other vaccines
- Potential impacts on antibiotic resistance

Alternative Immunization Strategies and Programs

- Existing recommendations/guidelines for use of the vaccine
- Objectives of disease control/elimination/eradication at international, national, and/or provincial/territorial levels
- Alternative immunization strategies for meeting objectives
- Specific objectives in terms of reduction of incidence, complications, sequelae and mortality
- Specific objectives re coverage of specific groups
- Delivery strategy/system

Social and Economic Costs and Benefits

- Total and opportunity costs of program for families and the health system
- Evidence regarding short- and long-term effectiveness
- Evidence regarding social and economic benefits
- Other benefits
- Economic evaluation: net present costs and cost-benefit ratios

Feasibility and Acceptability of Alternative Programs

- Public perception of disease risk, severity, fear, need for control
- Demand for/acceptability of immunization for target groups
- Priority for approved program compared with other programs
- Expected date of licensure or current use of vaccine
- Integration of new program with existing programs and schedules
- Impacts on existing immunizations services and the health care sector
- Accessibility of target population/expected levels of uptake
- Availability of vaccine supply
- Availability of funding for vaccine purchase
- Availability of human, technical and financial resources
- Availability of appropriate documentation/consent forms
- Availability of system for recording/registering vaccine administration
- Availability of resources for marketing and communication
- Existence of operational planning and implementation committee

Ability to Evaluate Questions

- Desirability of evaluation to families, professionals
- Availability of information systems to measure coverage, utilization, quality
- Availability of information systems for monitoring reduction of disease incidence, complications,, mortality
- Availability of system for monitoring adverse events associated with vaccine administration
- Availability of systems for linking health outcomes databases, immunization registries and population registries

Research Questions

- Ongoing and planned research projects in the fields of vaccine development, immunogenicity, efficacy and safety
- Identification of areas in previous sections in which research is needed to assist planning evaluation and decision-making

Other Considerations

- Equity of new program, including universality, accessibility and gratuity of services for the most vulnerable population groups
- Ethical considerations, including informed consent and protection of confidentiality of medical information
- Conformity of new program with planned or existing programs in other jurisdictions and countries
- Possible political benefits and risks associated with implementation of the new program

APPENDIX 2

Details and assumptions of the costs and utilities
Literature review of studies evaluating cost-effectiveness

Table 1a HPV vaccine cost-effectiveness studies, base case assumptions

Assumption	Sanders[36]	Kulasingam[35]	Goldie[38]	Brisson[40]	Taira[30]	Elbasha[32]	Marra[34]
Type of model	State-transition	State-transition	State-transition	State-transition	Hybrid	Dynamic	Dynamic
Vaccine target HPV types	13 high-risk HPV types	70% of high-risk HPV types	HPV 16/18	HPV 16/18 HPV 6/11/16/ 18	HPV 16/18	HPV 6/11/16/18	HPV 16/18
Vaccination age group	12 years old, female	12 years old, female	12 years old female	12 years old, female	12 years old, female ± male	12 years old, female ± male (± catch-up female ± male)	11 and 14-year-old females
Vaccination coverage	70%	100%	100%	100%	70%	70% (linear over first 5 years)	F11: 85% F14: 80%
Vaccination efficacy	75%	90%	90%	95%	90%	90%	100%
Duration of protection	10 years	10 years	Life long	Life long	10 years	Life long	Life long
Booster administration	Every 10 years	None reported	None	None	At 22 years old	None	None
Vaccine cost (three-dose administration)	$300 (2001 US$)	$200 (2001 US$)	$377 (2002 US$)	$400	$300 (2001 US$)	$360 (2005 US$)	$400
Booster cost	$100 (2001 US$)	–	–	–	$100 (2001 US$)	–	–
Outcomes measured*	HPV infection, SIL, cervical cancer, cervical cancer-related death, cost, life years, QALYs, cost per life year gained, cost per QALY gained	HPV infection, CIN, cervical cancer, cervical cancer death, cost, life years, cost per life year gained	HPV infection, LSIL, HSIL, cervical cancer, cost, QALYs, cost per QALY gained	HPV infection, CIN, cervical cancer, cervical cancer death, cost, life years, cost per life year gained	Cervical cancer, cost, life years, QALYs, cost per life year gained, cost per QALY gained	HPV infection, genital warts, CIN, cervical cancer, cost, QALYs, cost per QALY gained	HPV infection, CIN, cervical cancer, cervical cancer death, cost, life years, cost per life year gained
Perspective	Direct	Direct	Societal	Direct	Direct	Direct	Direct

*****SIL = squamous intraepithelial lesion, CIN = cervical intraepithelial neoplasia, LSIL = low-grade squamous intraepithelial lesion, HSIL = high-grade intraepithelial lesion

Table 1b HPV vaccine cost-effectiveness studies, results using case-base assumptions

Assumption	Sanders[36]	Kulasingam[35]	Goldie[38]	Brisson[40]	Taira[30]	Elbasha[32]	Marra[34]
Reduction in cervical cancer-related mortality	21%	–	–	–	–-	–	–
Reduction in cervical cancer cases	20%	15%	60%	62%	62% ♀ 64% ♀ & ♂	78% ♀ 91% ♀ & ♂	41% ♀ F14
Reduction in precancer lesions							
CIN 1	–	–	–	24%	–	–	
CIN 2/3	21%	–	–	47%	–	–	
Reduction in HPV infections	13%	–	–	–	95% ♀ 99% ♀ & ♂	–	75% ♀ F14
Reduction in genital warts cases	–	–	–	86%	–	83% ♀ 97% ♀ & ♂	–
Costs							
No vaccination	$39,682	$822	$1,111		$40,423	$72,659,302	$1,368,958,619
Vaccination	$39,928	$973	$1,400	7.2 million (Q)	$40 667	$74,042,990	$1,657,060,138
Δ Cost	$246		$289	4.4 million (B)	$244	$1,383,687	$288,101,519
Life years gained							
No vaccination	28.785 yr	28.756 yr	–	–	28.798 yr	–	–
Vaccination	28.793 yr	28.758 yr	–	–	28.811 yr	–	–
Δ LYG	2.8 yr		–	1,321 yr	5.0 yr	–	–
Quality-adjusted life years gained							
No vaccination	27.720 yr	–	25.982 yr	–	27.742 yr	2,698,711 yr	49,370,060 yr
Vaccination	27.731 yr	–	25.993 yr	–	27.759 yr	2,699,178 yr	49,381,805 yr
Δ QALY	4.0 yr	–	–	1,079 yr	6.1 yr	467 yr	11,744 yr
Cost /LYG	$32,066	$92,667	–	$34,496	$17,802	–	–
Cost /QALY	$22,755	–	$24,300	$20,512 Q $31,060 B	$14,583 ♀ $442,039 ♀ & ♂	$2,964 ♀ Dominated for ♀ & ♂	$24,530 ♀ F14 $167,364 ♀ & ♂

APPENDIX 3

Literature review
Ability to evaluate HPV vaccination programs

A literature review was carried out to document aspects of the evaluation of new HPV immunization programs. This literature review aimed to document item 7 of the decision-making model for vaccination[1]:

7. Can the various aspects of the program be evaluated?

    7.1 Desirability of evaluation to families, professionals, and political authorities
    7.2 Availability of information systems to measure coverage and vaccine utilization, quality of vaccination services
    7.3 Availability of information systems to measure impact of HPV-related infections
    7.4 Availability of information systems for monitoring adverse events associated with vaccine administration
    7.5 Availability of systems for linking health outcomes databases, immunization registries and population registries.

This literature review focused on evaluation outcomes specific to HPV vaccination programs. Aspects regarding the safety of licensed vaccines or duration of protection were not reviewed because they are usual outcomes considered in all evaluation studies following vaccine implementation programs. Data and publications related to HPV vaccination programs in developing countries were not reviewed.

The literature search was carried out using MEDLINE and Social Sciences Full Text databases. All publication types, but only articles written in French or English, were included. The search strategy combined the following key words:

MEDLINE, 4 July, 2007

Keywords used	Results	Kept
HPV vaccination program AND "Health care quality, access and evaluation"[87]	17	1
HPV immunization program AND "Health care quality, access and evaluation"[87]	131	1
HPV immunization AND Public health evaluation	57	0
HPV vaccine AND evaluation	133	1
HPV vaccine AND strategies	52	3
HPV vaccine AND surveillance	108	1
Human papillomavirus vaccination programs	69	3
HPV AND author: Lehtinen	15	1
Human papillomavirus AND author: Lehtinen	71	2
HPV AND author: Dillner	129	1
Human papillomavirus AND author: Dillner	150	0

All abstracts of publications from the databases were screened to assess their eligibility for inclusion. When articles could not be excluded on the basis of the abstract, the full-text version was obtained and screened. Additional searches were performed by using references from retrieved articles.

After review of the abstracts of those articles retained, only five met the eligibility criteria for this literature review (i.e. focused on HPV vaccination program evaluation, except for the aspect of safety and duration of protection of the vaccine). All publications were review articles, commentary, opinion pieces or guidelines, and none presented results of original research. The table below presents the main results of the literature review.

Literature review: evaluation of HPV immunization programs, July 2007

First author & Year	Type of publication	Specific HPV vaccination program outcomes to evaluate		Evaluation mechanism suggested to measure outcomes
		Short-term outcomes	**Long-term outcomes**	
Lehtinen (2006)[72]	Review, commentary, or opinion piece	• Vaccine efficacy against all cervical lesions independent of the HPV types • Changes in the prevalence of vaccine and non-vaccine HPV types in young women		• Serum samples obtained from pregnant women for population-based screening of congenital infections, together with cervical samples collected in organized screening for cervical cancer (Nordic healthcare/health registry infrastructure for long-term follow-up)
			• Effectiveness of different methods of implementing mass vaccination: o One or both sex vaccination strategies o Impact of catch-up vaccination strategies	• Evaluation of protective efficacy in community randomized trials, as originally described by Brookmeyer and Chen[88]
Arbyn (2007)[89]	Appendix to the European Guidelines on Quality Assurance in Cervical Cancer Screening	• HPV types in the population for early monitoring of "fill-in" phenomena, inappropriate vaccination strategies or other reasons for vaccination failure	• Protection against cancer measured by comparing the incidence of cervical and other HPV-associated cancers in vaccinated and non-vaccinated cohorts	• Linkage to cancer registries when possible. In anticipation of such results, estimations of the impact of HPV vaccination on the burden of cervical cancer incidence and mortality must be based on the observed surrogate endpoints (≥ CIN-3)

Saslow (2007)[73]	American Cancer Society Guideline		• Population- and lesion-based changes in type-specific prevalence of HPV types, including genital and non-genital HPV-associated tumors	
		• Tools to assist women and providers in making informed decisions about vaccination		
		• Abnormal Pap tests results, colposcopy referrals, cervical biopsies and genital warts	• Pap test performance (particularly positive and negative predictive value)	
			• Impact of vaccination on women's screening behaviour and provider behaviour • Vaccine acceptability and impact on sexual behaviour	• Qualitative and quantitative studies
		• Alternative vaccination strategies that increase access to the vaccine and expand the coverage of vaccination in populations		• Use of registries or other tracking data
Soldan (2006)[74]	Review, commentary, or opinion piece	• Monitoring and reporting of HPV infections (vaccine type and non-vaccine type) and HPV-associated diseases		• Utilization of internationally comparable methods; launching of an International HPV Laboratory Network (with a global reference laboratory in Malmö, Sweden) for HPV testing

			• Health impact of HPV vaccination programs	• International standardization of population-based reporting systems for major HPV-associated diseases with a baseline assessment of the total impact of HPV-associated diseases measured before the implementation of vaccination programs
Dillner (2007)[21]	Mini-review series on vaccine	• Levels of protective antibodies in vaccinated subjects		• Studies to define the minimum level of antibody levels required for protection
		• Population coverage of HPV vaccination		• If no HPV vaccination registries are available, the option is to perform sero-epidemiologic surveys to establish the vaccine-induced level of immunity in the population
		• HPV DNA prevalence in sexually active teenage populations		• Sentinel sampling in sexually active teenage populations in clinics offering sexual counselling to the youth to measure whether there is efficient control of HPV types included in the vaccines and whether the prevalence of non-vaccine HPV types is stable
		• Condyloma incidence		• Because 90% of condylomas are caused by HPV types included in the quadrivalent HPV vaccine, the disappearance of condylomas from the sexually active youth population is expected to be the first clinical outcome of HPV vaccination programs
		• Monitoring of whether or not remaining screen-detected lesions are attributable to HPV vaccine types		• HPV typing of lesions as part of screening program (HPV-type data for surveillance can be obtained from local laboratories performing HPV testing)
			• HPV-associated malignancies	• Routine HPV typing of all cases of HPV-associated cancer forms

APPENDIX 4

Pharmaco-economic evidence supporting the recommendations

For Canada, a cost-effective intervention is considered to be one in which the cost per quality-adjusted life year (QALY) gained is less than the per capita gross domestic product (approximately $40,000) and an extremely cost-effective intervention is considered to be one in which the cost per QALY gained is less than $20,000.

One female cohort selected from grade 4–8 (aged 9-14)

Grades 4 (9 years old) and 5 (10 years old): None of the cost-effectiveness studies on HPV vaccine published to date evaluated the impact of HPV vaccination in a 9- or 10-year-old. However, based on results from grades 6, 7 and 9 one would anticipate the program to be cost-effective, especially if there is an existing hepatitis B program on which the HPV could be piggybacked.

Grade 6 (11 years old): The model developed in British Columbia by Pourbohloul and Gunther[42] estimated that vaccination of 11-year-old girls (grade 6) would result in a decrease of 43.0% in HPV 16/18-related cervical cancer. The cost-effectiveness, calculated by Marra and colleagues[34], showed a cost of $24,945 per QALY gained compared with no vaccination. This program would be considered to be cost-effective.

Grade 7 (12 years old): All cost-effectiveness studies modelled in the United States published to date looked at the impact of vaccination of 12-year-old girls. Sanders and Taira[36] estimated a reduction of 20% in the incidence of cervical cancer at a cost of $22,755 per QALY gained with vaccination against 13 high-risk HPV types, as compared with no vaccination. Kulasingam and Myers[35] assumed vaccination against 70% of high-risk HPV types (including HPV 16/18) and obtained a 15% reduction in cervical cancer incidence at a cost of $92,677 per life year gained for vaccination (and biennial screening starting at age 18 years) compared with no vaccination. Goldie and colleagues[38] used a societal perspective in their model and estimated a 58.1% reduction in the incidence of cervical cancer at a cost of $24,300 per QALY gained with a bivalent vaccine against HPV 16/18 versus no vaccination. In the model by Taira[30], the incidence of cervical cancer was decreased by 61.8% at a cost per QALY gained of $14,583 with vaccination against HPV 16/18 compared with no vaccination. Finally, Elbasha et al.[32] assessed the impact of vaccination against HPV 6/11/16/18 and projected a decrease of 75% in the incidence of cervical cancer; this reduction was associated with an incremental cost per QALY of $2,964 compared with no vaccination. This program would be considered to be cost-effective.

Grade 9 (14 years old): The model developed in British Columbia by Pourbohloul and Gunther[37] estimated that vaccination of 14-year-old girls (grade 9) would result in a decrease of 41.0% in HPV 16/18-related cervical cancer. The cost-effectiveness calculated by Marra and colleagues[34] showed a cost of $24,530 per QALY gained compared with no vaccination. This program would be considered to be cost-effective.

Two female cohorts between grade 4 and grade 12

To date, none of the cost-effectiveness studies modeled in the United States looked at this type of vaccination strategy. For the BC model, Pourbohloul and Gunther[42] evaluated a program combining vaccination of 11-year-olds with 3 years of catch-up for 14-year-olds. With this program, the projected reduction in the incidence of cervical cancer was 46.0%. Marra and colleagues[34] showed a cost of $25,417 per QALY gained for this program compared with no vaccination. This program would be considered to be cost-effective.

School-based program, many cohorts (at minimum one cohort of girls from each elementary, junior and high school aged groups, i.e. a total of three cohorts).

To date, none of the cost-effectiveness studies modeled in the United States or Canada have evaluated this type of vaccination strategy. However, clinical studies have shown high immunogenicity in preadolescents and

adolescents aged 9-14[16]. A school-based program is also an effective way to obtain higher vaccination coverage at a lower cost.

All females for recommended ages of 9 to 26 years (option 1 is included in this option; this is a catch-up program)

Taira[30] estimated the reduction in lifetime risk of cervical cancer among 24-year-old women who received catch-up vaccination (35%), but unfortunately they did not calculate the costs associated with this strategy. Elbasha and colleagues[32] also evaluated the impact of three different vaccination strategies, including a catch-up program. One of these included female-only vaccination and looked at vaccination of 12-year-old girls with a catch-up program for females aged 12 to 24 years. The catch-up program was associated with a long-term reduction in the incidence of cervical cancer similar to that of the 12-year-old program only (~75% reduction). However, the decrease in the incidence was observed earlier with the catch-up program. Vaccination of 12-year-old girls with a catch-up program was associated with an incremental cost per QALY of $4,666 compared with vaccination of 12-year-olds only.

Appendix 5

Summary of CIC Recommendations

Routine immunization
To decrease the morbidity and mortality associated with cervical cancer, its precursors and other HPV-related cancers in women in Canada, the CIC recommends school-based HPV vaccination of one female cohort to be implemented in all Canadian provinces and territories. (a) To immunize 80% of school-aged girls in either grade 4, 5, 6, 7 or 8 with the required doses of the HPV vaccine within 2 years of program introduction. (b) To immunize 90% of school-aged girls in either grade 4, 5, 6, 7 or 8 with the required doses of the HPV vaccine within 5 years of program introduction. Particular efforts should be undertaken to achieve high vaccine coverage for routine programs in hard-to-reach and high-risk populations. Catch-up strategies could be extended to these populations.
Catch-up immunization
For jurisdictions that wish to and are able to consider catch-up programs could proceed with the inclusion of additional female cohorts. Particular efforts should be undertaken to achieve high vaccine coverage for routine programs in hard-to-reach and high-risk populations. Catch-up strategies could also be extended to these populations.
Immunization schedules
Following the manufacturers' indications for the quadrivalent HPV vaccine, NACI recommends a three-dose schedule (0, 2 and 6 months)[(2)].
Impact of vaccination on cervical cancer screening
The introduction of vaccination is expected to have a major impact ultimately on screening recommendations, and the two activities must now be planned simultaneously. An immunization program should constitute part of a comprehensive cervical cancer prevention program.
Program evaluation
To develop a detailed evaluation plan that would include: • Vaccination coverage; • Incidence and prevalence of HPV-associated diseases and cervical cancer; • Efficacy and duration of protection by the vaccine; • Psychosocial impact of vaccination; and • Optimal cervical cancer screening approaches.

Appendix 6

Abbreviations and acronyms

AB	Alberta
BC	British Columbia
BGTD	Biologics and Genetic Therapies Directorate
CAID	Community Acquired Infections Division
CCDPC	Center for Chronic Disease Prevention and Control
CCPCN	Cervical Cancer Prevention and Control Network
CFPC	College of Family Physicians of Canada
CHI	Canada Health Infoway
CIC	Canadian Immunization Committee
CIN	Cervical intraepithelial neoplasia
CIRN	Canadian Immunization Registry Network
CSCHAH	Canadian Science Center for Human and Animal Health
FNIHB	First Nations and Inuit Health Branch
F/P/T	Federal/provincial/territorial
GBS	Guillain-Barré Syndrome
GMT	Geometric mean titres
HPV	Human papillomavirus
IRID	Immunization and Respiratory Infections Division
MB	Manitoba
NACI	National Advisory Committee on Immunization
NB	New Brunswick
NICS	National Immunization Coverage Survey
NIS	National Immunization Strategy
NL	Newfoundland and Labrador
NT	Northwest Territories
NS	Nova Scotia
NU	Nunavut
NVPO-HHS	National Vaccine Program Office-Health and Human Services
ON	Ontario
OR	Odds ratio
P/T	Provincial/territorial
PE	Prince Edward Island
PHAC	Public Health Agency of Canada
QALY	Quality-adjusted life years
SK	Saskatchewan
SOGC	Society of Obstetricians and Gynaecologists of Canada
USA	Unites States of America
WHO	World Health Organization
YK	Yukon

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