Canadian Agency for Drugs and Technologies in Health

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Human Papillomavirus (HPV) Vaccines: A Canadian Update

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Summary

- **A common sexually transmitted infection, human papillomavirus (HPV) has been linked to the development of cervical, anogenital, and head and neck cancers and genital warts.**
- **Several randomized controlled trials have explored the efficacy and safety of two vaccines for primary prevention of infection by HPV types 16 and 18, those most commonly implicated in the development of cervical cancer.**
- **An HPV vaccine, Gardasil®, was approved in Canada in 2006, and a second vaccine, Cervarix®, is undergoing Health Canada review.**
- **Some unresolved questions about HPV vaccinations relate to the ideal age for immunization, duration of effect, immunization of women already infected, vaccination of males, implications for Papanicolaou (Pap) smear programs, barriers to uptake, need for monitoring and registries, cost-effectiveness, and programs to ensure access for special populations.**

Background

HPV is a common sexually transmitted infection capable of causing both benign and cancerous lesions. There are over 100 HPV types of which 25 to 40 infect the genital tract, including the cervix; an "oncogenic" subset of these is closely linked with cervical cancer.[1,2] Worldwide, HPV prevalence varies as does the proportion of cervical cancers caused by different HPV types.[3]

HPV 16 and 18 are among the high risk oncogenic HPV types, and together they are implicated in the development of 70% of cases of cervical cancer, with type 16 dominating at over 50%.[2,4] HPV has also been associated with the development of other anogenital cancers (vulva, vagina, anus, and penis) and some head and neck cancers.[5,6] Non-oncogenic HPV types such as 6 and 11 are linked to the development of 90% of cases of benign genital warts, lesions that are distressing although not life-threatening and that occur in 1% of the sexually active population.[7]

HPV infection affects about 550,000 Canadians annually, and at some point in their lives 80% of reproductive-age women will be infected.[2] It is most common in women between the ages of 16 and 24.[2,8,9] Over 50% of females acquire HPV within 48 months of becoming sexually active,[10] which generally occurs between ages 15 and 17.[11] Different HPV types are acquired, and these clear or persist independent of each other. No therapies exist to treat established HPV infection.[12] Most infections are symptom free and resolve spontaneously.[1,13] Being so ubiquitous, HPV infection is difficult to prevent in those who are sexually active. Decreasing the number of sexual partners and adopting safer sexual practices gives some protection. Vaccination offers a new option for primary prevention of HPV infection.[13]

The Technology

HPV is a viral particle made up of circular DNA molecules wrapped in a protein shell that generates an immune response through production of virus-neutralizing antibodies. This natural reaction formed the basis for the development of HPV vaccines that duplicate the antigen proteins using virus-like particles and stimulate the immune system without being pathogenic.[6,14] HPV vaccines have been found to induce an immune titre substantially higher than what occurs with natural immunity.[2,15] An adjuvant is incorporated into the vaccine to ensure an adequate immune response. The Gardasil vaccine

uses a proprietary aluminum hydroxyphosphate sulfate adjuvant.[16] Cervarix uses a proprietary adjuvant called "Adjuvant System 4" (AS04), promoted as serving both as an antigen carrier and an immunostimulant.[14]

Regulatory Status

Gardasil (Merck Frosst) is a recombinant quadrivalent vaccine approved for sale in Canada in July 2006. It is indicated for females aged 9 to 26 for the prevention of infection caused by HPV 6, 11, 16, and 18 and associated diseases, namely cervical cancer (including adenocarcinoma in situ); vulvar and vaginal cancer; cervical intraepithelial neoplasia (CIN) grades 1, 2, and 3; vulvar intraepithelial neoplasia grades 2 and 3; vaginal intraepithelial neoplasia grades 2 and 3; and genital warts.[17] European approval for Gardasil also covers its use in males aged 9 to 15 years.[16]

Cervarix (GlaxoSmithKline), a bivalent vaccine covering types 16 and 18, is currently under review by Health Canada.[18] Cervarix was granted its first licence in a major market in Australia, in May 2007, for prevention of cervical cancer and pre-cancerous lesions by HPV types 16 and 18 in females aged 10 to 45.[19] Cervarix received European Union approval in September 2007 for use in females aged 10 to 25.[20]

Patient Group

In Canada, approximately 1,340 women are diagnosed with cervical cancer each year and about 380 (28%) die from this disease.[21] For Canadian women aged 20 to 49, the disease is the third most common cancer,[5] although for Canadian women of all ages it drops to 11th place.[22] With respect to a prophylactic HPV vaccination program across the country (administered provincially), if females aged 9 to 26 were targeted as per the recommendations of Canada's National Advisory Committee on Immunization (NACI),[1] about 3.8 million Canadian girls and young women would be candidates for the vaccine.

Current Practice

The Pap smear is largely credited with the decline in cervical cancer incidence and death, with decreases of 50% to 80% where successful screening programs exist; however, the marked declines in disease incidence and mortality have slowed in recent years.[5,22,23] An effective Pap screening program prevents about 70% of cervical cancer cases[15] but has limitations. Due to low sensitivity rates, large numbers of abnormal smears are generated that require follow-up. For every case of invasive cancer discovered by Pap cytology there are up to 100 abnormal results that must be further investigated.[23]

The Evidence

A recent systematic review included six randomized controlled trials (RCTs) of the HPV vaccine (Table 1).[10] All were deemed to be high quality according to the scale developed by Jadad.[24] The studies collectively enrolled 40,323 women ranging in age from 15 to 25 years. Although the studies were conducted worldwide, most participants were Caucasian. The number of lifetime sexual partners of the participants was six or less, and 90% of enrolled women had no prior abnormal Pap test results.

Analysis of the likelihood of high-grade lesions (grade 2 CIN or worse) as reported in three RCTs (n=16,569) showed that, for every event that occurred in one vaccinated woman, 86 events occurred in women in the control groups. In women who received the vaccine, the pooled risk of having grade 2 CIN or worse ranged from 14% (95% confidence interval: 9% to 21%) in a per-protocol analysis to 52% (95% confidence interval: 43% to 63%) in a modified intention-to-treat meta-analysis as compared with the risk observed in the unvaccinated control groups.

Analyses of secondary outcomes (any CIN, persistent HPV infection, and external genital disease) also favoured the vaccine. The authors concluded that prophylactic HPV vaccination was efficacious in preventing HPV infection and precancerous cervical disease caused by the HPV types covered by the vaccine, particularly for women aged 15 to 25 years who received all three vaccine

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Table 1: Randomized controlled trials of HPV vaccines						
Study	**Koutsky *et al.*, 2002 (f/u Mao *et al.*, 2006)**	**Harper *et al.*, 2004 (f/u Harper *et al.*, 2006)**	**PATRICIA, 2007 (interim analysis)**	**Villa *et al.*, 2005 (f/u Villa *et al.*, 2006)**	**FUTURE I, 2007**	**FUTURE II, 2007**
Vaccine type	Monovalent HPV 16	Bivalent HPV 16 and 18	Bivalent HPV 16 and 18	Quadrivalent 6, 11, 16, and 18	Quadrivalent 6, 11, 16, and 18	Quadrivalent 6, 11, 16, and 18
Study funding	Merck	GSK	GSK	Merck	Merck	Merck
Commercial name	Not commercialized	Cervarix	Cervarix	Gardasil	Gardasil	Gardasil
Vaccine adjuvant	Aluminum hydroxy-phosphate sulfate	AS04	AS04	Aluminum hydroxy-phosphate sulfate	Aluminum hydroxy-phosphate sulfate	Aluminum hydroxy-phosphate sulfate
n=	2,392	1,113	18,644	552	5,455	12,167
Study phase	2	2	3	2	3	3
Comparator	Placebo	Placebo	Hepatitis A vaccine	Placebo	Placebo	Placebo
Period of recruitment	1998-1999	Initial study 2000-2001; f/u study 2003-2004	2004-2005	2000-2004	2002-2003	2002-2003
Country of recruitment	US	US, Canada, Brazil	14 countries including Canada	US, Brazil, Sweden, Finland, Norway	16 countries including Canada	13 countries (not Canada)
Mean age, years (range)	20 (16 to 23)	20 (15 to 25)	20 (15 to 25)	20 (16 to 23)	20 (16 to 24)	20 (15 to 26)
Study duration and follow-up	Initial study, median 17.4 months; f/u study mean 42 months	Initial study, 18- and 27-month endpoints; f/u study mean 47.7 months	Mean 14.8 months	Initial study, mean 35 months; f/u study mean 60 months	48-month study; reported data for 3-year mean	48-month study; reported data for 3-year mean
Modified ITT meta-analysis results: OR (95% CI) for vaccine group	Persistent HPV at 6 months: 0.15 (0.10 to 0.21)* Grade CIN 2 or worse: 0.28 (0.13 to 0.59) Any CIN: 0.24 (0.14 to 0.42)	Persistent HPV at 12 months: 0.16 (0.06 to 0.42) Grade CIN 2 or worse: 0.13 (0.02 to 0.76) Any CIN: 0.13 (0.03 to 0.52)	Persistent HPV at 12 months: 0.29 (0.18 to 0.50) Grade CIN 2 or worse: 0.19 (0.082 to 0.44) Any CIN: 0.20 (0.10 to 0.40)	Persistent HPV at 6 months: 0.14 (0.08 to 0.23) Any CIN: 0.13 (0.03 to 0.58) External genital lesions: 0.13 (0.02 to 0.94)	Grade CIN 2 or worse: 0.65 (0.46 to 0.92) External genital lesions: 0.31 (0.22 to 0.44)	Grade CIN 2 or worse: 0.56 (0.43 to 0.73) Any CIN: 0.46 (0.35 to 0.60)

* Per-protocol analysis. CIN=cervical intraepithelial neoplasia; f/u=follow-up; GSK=GlaxoSmithKline; HPV=human papillomavirus; OR=odds ratio.
Table adapted from Rambout *et al.*, 2007[10] and Franco and Ferrencz, 2007.[23]

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doses, had six or fewer lifetime sexual partners, and had no prior abnormal Pap results.[10]

These studies had a number of limitations. Outcomes such as cervical cancer incidence or mortality were not evaluated. The generalizability of the studies may be limited by the homogeneity of study participants and vaccine coverage of only two of the many oncogenic HPV strains. Loss to follow-up was relatively high and the length of follow-up was insufficient to determine duration of vaccine efficacy.

Adverse Effects

Local injection site symptoms (pain, swelling, or redness) occur in up to 90% of recipients, and systemic adverse events such as headache, fatigue, gastrointestinal upset, and rash occur in 69% to 86% of recipients, although these are only partially attributable to vaccination.[16] In the Gardasil trials, serious adverse events (SAEs), including headaches, gastroenteritis, appendicitis, and pelvic inflammatory disease, were reported in 0.48% of recipients.[10] The rate did not differ between vaccine and control groups, and no deaths were attributed to the vaccine.[10] A possible association between Gardasil vaccination and Guillian-Barre Syndrome, an autoimmune disorder, is being investigated by the US Vaccine Adverse Event Reporting System (VAERS). With its US approval in June 2006, Merck committed to a safety surveillance study that is due to report in 2009 and monthly and quarterly adverse event reporting for the first three years post-licensing.[25]

Administration and Cost

Both Gardasil and Cervarix are administered intramuscularly in a three-dose regimen over six months. The need for subsequent boosters is unknown. Vaccine costs for Gardasil are currently at least C$400 for the three-dose course.[22,26] In addition, informing and educating patients, families, and providers must be factored into program costs, as must staffing and program delivery.

A recent Canadian cost-effectiveness analysis projected the medium- to long-term impact of HPV vaccination. As a ministry of health perspective was taken, only direct costs (in 2005 dollars) were included.[5] Costs per quality-adjusted life year (QALY) calculations differed according to the duration of immunity (Table 2). Vaccine costs had a major influence; each increase (or decrease) of C$50 per vaccine dose of the bivalent or quadrivalent vaccine produced an increase (or decrease) of C$4,000 and C$3,000, respectively, per QALY gained. Differences in QALYs with the bivalent and quadrivalent vaccines were due to prevention of genital warts and low grade cervical disease with the quadrivalent vaccine. In addition, the analysis concluded that:

- Immunizing males was not cost-effective unless coverage rates in women were low.
- Vaccine coverage rates of 60% or better were required to decrease cervical cancer rates.
- A lag of 60 years was required before a significant reduction in cervical cancer was observed.
- Cost-effectiveness improved if Pap screening started later and intervals were widened.
- Vaccine effectiveness, duration of protection, cost, the health utilities used to estimate QALYs, and the inclusion of males in an immunization program all influenced the analyses.

Three additional Canadian economic evaluations were identified:

- A BC Cancer Agency background paper cited cost-effectiveness data in the range of $45,000

Table 2: Cost-effectiveness of HPV vaccines according to duration of immunity[5]

	Bivalent (16/18) vaccine Cost per QALY*	**Quadrivalent (6/11/16/18) vaccine Cost per QALY***
Lifelong duration of vaccine protection	$31,060	$20,512
30-year duration	$114,846	$64,584
30-year duration with booster	$56,028	$36,981

*QALY=quality-adjusted life year

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to $60,000 (2002 US dollars) per QALY for a combined vaccination and screening program that would reduce lifetime cervical cancer mortality by 90%. Calculated costs for BC to introduce a quadrivalent vaccine program for 12-year-old girls with 80% uptake, 100% vaccine efficacy, and a $300 vaccine cost for three doses would cost about $6M in Year 1, but would avoid no medical costs. Projecting out, by Year 26 there would be $8.2M in program costs and $3.6M in medical costs avoided.[27]

- A 2007 analysis from the BC Centres for Disease Control concluded that, compared with no vaccination, a combined Grades 6 and 9 program vaccinating girls against HPV types 16 and 18, with vaccine costs of about $150 per dose, would be cost-effective with an incremental cost of $25,000 per QALY, provided the duration of protection is lifelong. Immunizing boys was not cost-effective with a projected incremental cost per QALY of $167,000.[28]

Concurrent Developments

HPV types other than 16 and 18 are also implicated in cervical cancer development, and vaccine manufacturers are hoping to expand protection beyond the 70% of cervical cancers covered by the current vaccines.[12] There is some evidence that both Gardasil and Cervarix also offer cross-protection against oncogenic HPV types 31 and 45.[4,16,29,30] New types of vaccines are being explored, for example "capsomere-based" products that are smaller in size, more stable, and easier to produce.[4] Two-dose vaccine regimens are also being studied.[31]

With respect to therapeutic vaccines for people already infected with HPV, various methods and forms of delivery are being investigated. Although safety and immunogenicity have been noted, none of the technologies has yet proven its worth.[4,6,8,11,32] Aside from vaccine development, directly detecting HPV in cervical cells has been proposed as a measure of cancer precursor risk, but currently available applications are not clinically useful.[2,12]

Rate of Technology Diffusion

Canada's federal budget of March 2007 committed C$300M over two years to establish provincial and territorial HPV vaccination programs. British Columbia, Ontario, PEI, Nova Scotia, and Newfoundland and Labrador have thus far stated intentions to launch immunization of girls in Grades 6, 7, or 8 in the 2007/2008 or 2008/2009 school year.[33] Worth noting is the potential for expansion of vaccine use to populations not covered by vaccine programs or outside of the age groups indicated in the regulatory approval.

Implementation Issues

Potential implementation issues with the HPV vaccines include:

- *Age at vaccination:* In February 2007, the Canadian National Advisory Committee on Immunization recommended immunization of females aged 9 to 13 before the onset of sexual intercourse, where the efficacy would be the greatest, and also those aged 14 to 26, recognizing that the latter group may already be infected with one or more HPV types.[1] Relatively few pre-adolescent and young adolescent girls (about 1,200 from 9 to 15 years of age in the Gardasil trials) have been observed post-vaccination, yet this age group is the one primarily targeted for vaccination.[22]
- *Duration of vaccine effect:* Studies have followed those immunized for only up to 5.5 years.[10] It is currently unknown how long effective immunity will last after five years and whether boosters will be required. Analyses of long-term benefits and costs are complicated by this uncertainty.[34]
- *"Catch-up" vaccination programs:* To benefit the group of females most actively spreading HPV infection (ages 16 to 20), catch-up immunization programs are being considered for those not yet infected and, for females already infected, to cover HPV types not yet present.
- *Effectiveness in special groups:* High uptake in lower socioeconomic populations is important, as these women currently have the highest rates of cervical cancer in part due to

less-than-ideal rates of Pap screening.[35] Access must be assured for marginalized and vulnerable groups of women.[22]

- *Lifetime number of sexual partners:* Exposure to HPV infection is closely linked to lifetime number of sexual partners.[11] Vaccine benefits for women with more than six partners in their lifetime are unknown, as this group has not been studied.
- *Herd immunity:* Immunization aims to render a population resistant to an infectious agent, or eradicate it completely, by protecting the vast majority of individuals.[26] With HPV vaccination, herd immunity will require several generations, because many women are persistently infected and a therapeutic vaccine does not yet exist. As well, men will continue to act as HPV reservoirs.[16]
- *Immunizing males:* The utility of immunizing males is dependent on levels of vaccination achieved in females; for example, if all females are protected, transmission of high-risk HPV types from males is not a concern.[8] Male vaccination may be cost-effective if vaccine rates in eligible women are less than ideal or vaccine efficacy wanes.[16,36] Potentially, men could directly benefit from HPV vaccination in reducing risk of genital warts as well as anal, penile, and oropharyngeal cancers if further research shows a benefit.[4] Considerations of cost-effectiveness would be a separate matter.
- *Need for ongoing Pap screening:* Over time the introduction of HPV vaccination will have significant implications for Pap screening programs; for example, screening may start at a later age (mid-20s) with intervals widening to 3 to 5 years, depending on current screening intervals.[8,15] Concern has been expressed that screening participation may drop as the incidence and awareness of cervical cancer decrease or if women erroneously believe they are totally protected.[16,22] Due to the lag between vaccination and cancer prevention, long-term monitoring will be required to ensure that the expected health gains are realized and that Pap and any other screening protocols in the future are optimal.[8,37]
- *Vaccine uptake:* HPV vaccination is expected to be implemented on a voluntary rather than a mandatory basis to allow for parental and religious differences regarding teenage sexuality, anti-vaccine opinions, and concerns about long-term effectiveness or safety.[16,38]
- *Monitoring vaccination programs:* To determine the impact and value of an HPV vaccination program, attention must focus on long-term monitoring of outcomes such as vaccine uptake, follow-up screening, cancer incidence, and cost-effectiveness.[35,38]
- *Changing proportions of oncogenic types:* It is unknown how vaccination against HPV types 16 and 18 could change the distribution of other high-risk HPV types.[16] As immunization suppresses specific HPV types, those not suppressed may gain an evolutionary advantage and become more prevalent or even dominant.[26] Such "type replacement" could occur only if there is partial competition between HPV types during natural infection and vaccines do not lead to cross-protection against competing HPV types.[8] Although there is no indication that this is a critical area of concern, it may still be ideal to work towards a pan-HPV vaccine, but given the current state of the science and technological development this does not appear to be imminent.[7]
- *Variation in HPV type distribution:* The relative proportions of HPV types vary around the world and in different ethnic populations. This is also true of the proportion of HPV types implicated in cervical cancer, a fact that may have implications for health services required for immigrant cohorts and other specific populations.

The Canadian Immunization Committee is planning to publish recommendations related to HPV vaccination late in 2007.[22]

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