The Human Papillomavirus Vaccine in Canada

Shaun K. Morris, MD, MPH¹

Claire K. Nguyen, BNSc, MSc, LLB, MPH²

ABSTRACT

Clinical studies have shown the human papillomavirus (HPV) vaccines to be very effective at preventing persistent infection by vaccine serotypes. The development of these new vaccines heralds a new era in cancer prevention. Gardasil, Merck's quadravalent HPV vaccine, has recently been licensed in Canada for women aged 9 to 26 years of age. It necessitates that health professionals become familiar with the vaccine, the evidence supporting its effectiveness and issues related to vaccine strategy, cost effectiveness, and remaining research questions. The vaccine is recommended in Canada for females aged 9 to 13 years and should also be offered to females aged 14 to 26 years. Ongoing research will determine the duration of protection conferred by the vaccine, and the potential need for booster doses. In conjunction with continued screening programs, the HPV vaccine offers the potential to dramatically reduce the burden of cervical cancer in Canada, and to do so in a cost-effective manner.

Key words: Human papillomavirus; cervical neoplasms; vaccines; public health; Canada

RÉSUMÉ

Des études cliniques ont montré que les vaccins contre le virus du papillome humain (VPH) sont très efficaces pour prévenir les infections persistantes par les sérotypes vaccinaux. La mise au point de ces vaccins annonce une ère nouvelle pour la prévention du cancer. Gardasil, le vaccin quadrivalent anti-VPH de Merck, a récemment été homologué au Canada pour les filles et les femmes de 9 à 26 ans. Il faut cependant que les professionnels de la santé se familiarisent avec le vaccin, les preuves de son efficacité, la stratégie de vaccination, le rapport coût-efficacité et les questions de recherche non résolues. Au Canada, le vaccin est recommandé pour les filles de 9 à 13 ans et devrait aussi être offert aux filles et aux femmes de 14 à 26 ans. Des recherches en cours permettront de déterminer la durée de la protection conférée par le vaccin et les doses de rappel nécessaires, le cas échéant. Utilisé conjointement avec les programmes de détection en cours, le vaccin anti-VPH présente la possibilité de réduire considérablement le fardeau du cancer du col utérin au Canada, et de le faire de façon économiquement rentable.

Mots clés : virus du papillome humain; néoplasmes cervicaux; vaccins; santé publique; Canada

High-risk types of human papillomavirus (HPV) are the causal agents of more than 99% of cervical cancer cases.^{1,2} Of the more than 100 types of HPV, there are approximately 13 to 18 serotypes that are linked to cervical cancer.² Two types, HPV 16 and HPV 18, are associated with over 70% of cases of cervical cancer.³ HPV is also associated with other types of malignancies including anal^{4,5} and penile cancer,⁵ as well as genital warts in both males and females.⁶ Two serotypes, HPV 6 and 11 cause approximately 90% of anogenital warts.

A high percentage of women are infected with HPV soon after sexual debut.⁷ The Public Health Agency of Canada estimates that high-risk types of HPV have a prevalence of 11-25% in the general female population, and over 50% in some high-risk populations including First Nations, recent immigrants, and women of lower socio-economic standing.⁸

The incidence of cervical cancer has been dramatically reduced in the developed world due to routine screening for abnormal cells with the Papanicolaou (Pap) smear. While specific guidelines vary from country to country, they generally call for smears in sexually active women over the age of 18 every one to three years.⁹ However, in Canada, 16% of all women over the age of 18 had never had a smear, and 35% of women aged 18 to 24 had never had a smear.⁹ Certain groups, including First Nations women, the homeless, and sexually active teenagers, are at particular risk for not receiving Pap smears as recommended. It is estimated that in Canada, there are 1,350 new cervical cancer cases and approximately 400 deaths each year.¹⁰

HPV vaccine clinical trials

The HPV vaccines consist of HPV virus-like particles based on the major capsid antigen L1.³ Clinical trials, sponsored by both Merck (quadravalent vaccine HPV 6, 11, 16, and 18) and GlaxoSmithKline (GSK) (bivalent vaccine HPV 16 and 18) have demonstrated high levels of vaccine-induced protection against persistent infection by vaccine serotype HPV strains (Table I). Both vaccines were tested using a three-dose schedule – the quadravalent Merck vaccine at 0, 2, and 6 months and the bivalent GSK vaccine at 0, 1, and 6 months. None of the trials have reported

1. Division of Infectious Diseases, The Hospital for Sick Children and The University of Toronto, Toronto, ON

2. Registered Nurse, Mount Sinai Hospital, Toronto

Correspondence and reprint requests: Dr. Shaun K. Morris, Division of Infectious Diseases, The Hospital for Sick Children, 555 University Avenue, Toronto, ON M5G 1X8, Tel: 416-813-7500, E-mail: shaun.morris@utoronto.ca

TABLE I
Randomized, Placebo-controlled Trials of HPV Vaccine Efficacy

Study Sponsor	HPV Serotypes	Timing of Vaccination (months)	Age of Women Included (years)	Duration of Study (months)	Protection Against Persistent Infection (95% CI)
Merck ¹²	16	0,2,6	16-23	17	100% (90-100)
Merck ¹³	16	0,2,6	16-23	36	100% (85-100)
Merck ¹⁴	6,11,16,18	0,2,6	16-23	35	89% (70-97)
GSK ¹⁵	16,18	0,1,6	15-25	27	74% (50-86)
GSK ¹⁶	16,18	0,1,6	15-25	48	94% (63-100)

TABLE II
Top 10 Research Areas Related to HPV Vaccine in Canada¹⁷

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

any major adverse effects of the vaccine. On July 11, 2006, Health Canada approved Merck's quadravalent HPV vaccine, Gardasil, for immunization of women aged 9 to 26 years.¹¹

Immunization strategy and program

The HPV immunization strategy in Canada must take into account the existing vaccine schedule, the age-related risk of HPV, and the currently unknown duration of protection provided by the vaccine. Clinical trials to date have included females between the ages of 9 and 26 years, and it is for this age range that the vaccine has been licensed in Canada.¹²⁻¹⁶ Based on available clinical information, persistent infection with the highest-risk subtypes of the virus may be completely prevented if administered within this window. The Canadian National Advisory Committee on Immunization (NACI) has recently recommended Gardasil for females aged 9 to 13 years and also states that females aged 14 to 26 years would benefit from the vaccine even if they are already sexually active.¹⁷

Incorporating this new vaccine in a three-dose schedule into an already complex pediatric vaccination schedule will require co-ordination and integration with existing immunization timetables. The HPV vaccine may be offered most easily in provinces that offer hepatitis B vaccine to schoolchildren between grades 4 through 7. Currently, all Canadian provinces have hepatitis B vaccine uptake rates of over 90%.¹⁸ By delivering the HPV vaccine

along with hepatitis B vaccine, the HPV vaccine may experience similar uptake rates.

Cost-effectiveness of the program

A full cost-effectiveness analysis of HPV vaccines has not been conducted in the Canadian context. Several studies in the United States have used complex decision models to examine the cost-effectiveness of the HPV vaccine targeted at pre-adolescent girls. Though the studies differed in assumptions about vaccine coverage, efficacy, duration, and cost, all concluded that in conjunction with continued screening programs, the vaccine can be cost effective.¹⁹⁻²² Taira et al.²⁰ calculated a cost per quality adjusted life year (QALY) of \$14,583 for a female-only vaccination strategy. It was estimated that the inclusion of males would further reduce cervical cancer cases by 2.2%, but at a cost-effectiveness ratio of \$442,039 per QALY compared to female-only vaccination.²⁰

Acceptability of vaccine program

Universal acceptance of the HPV vaccine is not assured. Some parents may believe their child is not at risk for a sexually transmitted infection. Others may feel that the vaccine could result in an increase in adolescent sexual activity. Some parents may object to the vaccine on other moral, religious, or philosophical grounds.²³⁻²⁷ However, multiple studies have shown that parental acceptance of the HPV vaccine may be increased through education

regarding the virus and its relation to cervical cancer.^{26,27} Evidence suggests that concerns regarding increased adolescent sexual activity are unfounded and that these apprehensions may be effectively addressed through anticipatory guidance.^{24,27}

Remaining questions

While the clinical evidence strongly suggests that HPV vaccines confer protection against persistent infection by high-risk HPV serotypes, there are not yet data confirming a decrease in the incidence of cervical cancer. However, a recent randomized prospective study has shown the quadravalent HPV vaccine to have 100 (86-100) and 97 (79-100) efficacy, in fully vaccinated individuals, in preventing HPV 16 and 18 associated grade 2 and 3 intraepithelial neoplasia, respectively.²⁸ Long-term prospective studies will be required to confirm the expected decrease in incident cancer in vaccine recipients.

At present, the duration of protection conferred by the HPV vaccine is not known. A Merck-sponsored study documents protection against persistent infection with stable antibody levels 60 months from time of vaccination.²⁹ Ongoing pharmaceutical-sponsored studies will persist if this level of protection continues indefinitely or wanes with time.

The HPV vaccine is currently licensed only in females. Vaccination of males may provide further protection to females through reduction of transmission via the male vector, as well as reduce HPV-related disease in this gender. However, because morbidity and mortality due to HPV is rare in males, the risk-to-benefit ratio of the vaccine significantly differs by gender. The present evidence does not support mass vaccination of males.

Continued Pap screening, post-vaccine introduction, remains important as the vaccine does not provide protection against all cancer-causing HPV serotypes, nor will it provide protection for those currently infected or those who already have pre-malignant or malignant cellular changes. The effect of introduction of the vaccine on screening trends and behaviours is not known.

Also to be addressed is how to best target hard-to-reach, high-risk populations. Any immunization program that does not actively take measures to offer accessible

and affordable vaccination to high-risk populations will achieve a less than desirable population-level impact on cervical cancer incidence rates. It will be inherently difficult to fully immunize hard-to-reach populations with a three-dose vaccine schedule. NACI has identified the immunogenicity of the two-dose series as well as the need for ongoing research to evaluate the introduction and impact of the vaccine in Canada. A HPV Vaccine Research Priorities workshop in 2005 identified the 10 highest-ranked research questions regarding the use of HPV vaccine in Canada (Table II).

The global perspective

Cervical cancer is the second most common cancer in women worldwide and approximately 80% of the nearly 300,000 cervical cancer-related deaths each year occur in the developing world.³⁰ In many regions, women do not have ready access to cervical cancer screening. At its current cost, the HPV vaccine will be prohibitively expensive for much of the global population. The historical experience with the hepatitis B vaccine indicates that the poor may not gain access to the HPV vaccine. The hepatitis B vaccine has been available for nearly a quarter of a century and is recommended by the World Health Organization's Expanded Program on Immunization. However, it is estimated that approximately 2 billion people are infected with hepatitis B worldwide and that there are 500,000 to 1.2 million deaths per year, 320,000 from hepatocellular cancer due to the virus.³¹ Vaccine developers, producers, and policy-makers must consider new ways of reducing the cost of the HPV vaccine and developing formulations and logistics that ensure an equitable distribution of this potential life-saving product throughout all parts of the world.

CONCLUSION

Merck's HPV quadrivalent vaccine, Gardasil, has been approved by Health Canada for immunization of women aged 9 to 26 years and it is expected that GSK's vaccine will be approved in the near future. The success of the HPV vaccine in preventing persistent infection and grades 2 and 3 cervical intraepithelial neoplasia in clinical trials, and the resultant potential

ramifications for cervical cancer incidence, heralds an exciting new era in cancer prevention. The initial program strategy in Canada is to offer vaccination to young adolescent females prior to common age of sexual debut. In conjunction with continued screening programs, the HPV vaccine offers the potential to significantly reduce the burden of cervical cancer in Canada.

REFERENCES

- Monsonogo J, Bosch FX, Coursaget P, Cox JT, Franco E, Frazer I, et al. Cervical cancer control, priorities and new directions. *Int J Cancer* 2004;108(3):329-33.
- Spence AR, Franco EL, Ferenczy A. The role of human papillomaviruses in cancer: Evidence to date. *Am J Cancer* 2005;4(1):49-64.
- Cohen J. High hopes and dilemmas for a cervical cancer vaccine. *Science* 2005;308:618-21.
- Hernandez BY, McDuffie K, Zhu X, Wilkens LR, Killeen J, Kessel B, et al. Anal human papillomavirus infection in women and its relationship with cervical infection. *Cancer Epidemiol Biomarkers Prev* 2005;11(1):2550-56.
- van der Snoek EM, Niesters HG, Mulder PG, van Doornum GJ, Osterhaus AD, van der Meijden WJ. Human papillomavirus infection in men who have sex with men participating in a Dutch gay-cohort study. *Sex Transm Dis* 2003;30(8):639-44.
- Leung AK, Kellner JD, Davies HD. Genital infection with human papillomavirus in adolescents. *Adv Ther* 2005;22(3):187-97.
- Moscicki AB, Shiboski S, Broering J, Powell K, Clayton L, Jay N, et al. The natural history of human papillomavirus infection as measured by repeat DNA testing in adolescent and young women. *J Pediatr* 1998;132:277-84.
- Public Health Agency of Canada. STI Epi Update. Available online at: http://www.phac-aspc.gc.ca/publicat/epiu-aeipi/std-mts/hpv_e.html (Accessed March 2, 2006).
- Programmatic Guidelines for Screening for Cancer of the Cervix in Canada. Society of Gynecologic Oncologists of Canada and Health Canada, 1998. Available online at: <http://www.phac-aspc.gc.ca/ccdpc-cpcmc/cc-cu/pdf/screening.pdf> (Accessed March 3, 2006).
- Canadian Cancer Society. Canadian Cancer Statistics 2005. Available online at: http://www.ncic.cancer.ca/vgn/images/portal/cit_86751114/60/42/393678947ncic_2005stats_en.pdf (Accessed March 2, 2006).
- Public Health Agency of Canada. Human Papillomavirus (HPV) Prevention and HPV Vaccine: Questions and Answers. Available online at: http://www.phac-aspc.gc.ca/std-mts/hpv-vph/hpv-vph-vaccine_e.html (Accessed November 15, 2006).
- Koutsky LA, Ault KA, Wheeler CM, Brown DR, Barr E, Alvarez FB, et al. A controlled trial of a human papillomavirus type 16 vaccine. *N Engl J Med* 2002;347:1645-51.
- Mao C, Koutsky LA, Ault KA, Wheeler CM, Brown DR, Wiley DJ, et al. Efficacy of human papillomavirus-16 vaccine to prevent cervical intraepithelial neoplasia: A randomized controlled trial. *Obstet Gynecol* 2006;107(1):18-27.
- Villa LL, Costa RL, Petta CA, Andrade RP, Ault KA, Giuliano AR, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: A randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol* 2005;6(5):271-78.
- Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuid A, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: A randomised controlled trial. *Lancet* 2004;364(9447):1757-65.
- Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins CM, et al. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: Follow-up from a randomized control trial. *Lancet* 2006;367(9518):1247-55.
- The National Advisory Committee on Immunization (NACI). Statement on Human Papillomavirus Vaccine. *Canada Communicable Disease Report* 2007;33 ACS-2:1-32.
- Scheifele D. Universal childhood hepatitis B vaccination: Infants vs. preadolescents, the Canadian perspective. *Pediatr Infect Dis J* 1998;17(7 Suppl):S35-S37.
- Sanders GD, Taira AV. Cost-effectiveness of a potential vaccine for human papillomavirus. *Emerg Infect Dis* 2003;9(1):37-48.
- Taira AV, Neukermans CP, Sanders GD. Evaluating human papillomavirus vaccination programs. *Emerg Infect Dis* 2004;10(11):1915-23.
- Goldie SJ, Kohli M, Grima D, Weinstein MC, Wright TC, Bosch FX, Franco E. Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. *J Natl Cancer Inst* 2004;96(8):604-15.
- Kulasingam SL, Myers ER. Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. *JAMA* 2003;290(6):781-89.
- Brabin L, Roberts SA, Farzaneh F, Kitchener HC. Future acceptance of adolescent human papillomavirus vaccination: A survey of parental attitudes. *Vaccine* 2006;24(16):3087-94.
- Zimet GD, Mays RM, Fortenberry JD. Vaccines against sexually transmitted infections: Promise and problems of the magic bullets for prevention and control. *Sex Transm Dis* 2000;1:49-52.
- Humiston SG, Rosenthal SL. Challenges to vaccinating adolescents: Vaccine implementation issues. *Pediatr Infect Dis J* 2005;24(6 Suppl):S134-40.
- Davis K, Dickman ED, Ferris D, Dias JK. Human papillomavirus vaccine acceptability among parents of 10 to 15 year old adolescents. *J Low Genit Tract Dis* 2004;8(3):188-94.
- Zimet GD, Liddon N, Rosenthal SL, Lazcano-Ponce E, Allen B. Psychosocial aspects of vaccine acceptability. *Vaccine* 2006;24(Suppl 3):S201-9.
- The Future II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007;356(19):1915-27.
- Villa LL, Costa RL, Petta CA, Andrade RP, Paavonen J, Iversen OE, et al. High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. *Br J Cancer* 2006;95(11):1459-66.
- World Health Organization. Cervical Cancer Screening in Developing Countries. Available online at: <http://whqlibdoc.who.int/publications/2002/9241545720.pdf> (Accessed November 15, 2006).
- Lavanchy DJ. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. *J Viral Hepat* 2004;11(2):97-107.

Received: November 21, 2006

Accepted: October 3, 2007