

# The Postal Code Lottery of Human Papillomavirus Vaccination in Canada



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## Background

Human papillomavirus (HPV) is one of the most prevalent sexually transmitted infections in Canada, with nearly 75 per cent of sexually active men and women having at least one infection in their lifetime.<sup>1</sup> In addition to causing genital warts, infection with HPV has been linked to various malignancies, the most infamous being cervical cancer which is caused almost exclusively by infection with HPV. However, HPV is also a major cause of malignancy in both men and women, including anal and oropharyngeal cancers, as well as penile cancer in men. Male cancers related to HPV, although rare, still represent a significant burden and their incidence is on the rise.<sup>2</sup>

Multiple HPV strains are capable of causing anogenital infection and the majority of immunocompetent adults are able to successfully clear the virus without any long-term sequelae. However, chronic infection with certain high-risk oncogenic strains, notably HPV types 16 and 18, has been implicated in roughly 70 per cent of cervical cancers, 88 per cent of anal cancers, 61 per cent of oropharyngeal cancers and 50 per cent of penile cancers.<sup>3</sup> In men specifically, 92 per cent of anal cancers, 63 per cent of penile cancers, and 89 per cent of oropharyngeal cancers are attributable to HPV types 16 and 18. HPV types 6 and 11 cause nearly 90 per cent of genital warts.<sup>4</sup>

Two recombinant, adjuvanted vaccines are commercially available in Canada; a quadrivalent vaccine against HPV

types 6, 11, 16 and 18 (Gardasil) and a bivalent vaccine against HPV types 16 and 18 (Cervarix). Both vaccines are Health Canada approved for females between the ages of nine and 45 for protection against the development of precancerous and cancerous lesions of the cervix. A detailed comparison may be found in Table 1.

The differing indications for cancer prevention are unlikely to be clinically relevant, not only for biological reasons, but clinical trials have shown both the bivalent and quadrivalent vaccines to be effective in girls and women.<sup>5</sup>

## Cost-Efficacy

Cost-efficacy analyses are so far inconclusive, with some for and against expanding HPV vaccination programs to include males. Most Canadian cost-efficacy analyses are unable to recommend expanding vaccine programs to males, unless uptake in females is less than 50 per cent, and instead encourage increased uptake in females as a more cost-effective strategy.<sup>6</sup> However, the Public Health Agency of Canada warns that the quality of life and economic burden of HPV-related disease in Canadian males is significant and should be considered when reviewing vaccination programs.<sup>4</sup>

Keeping this in mind, there has been a lower than desired uptake of HPV vaccine with 2011-2012 data showing only 70 per cent of eligible females were vaccinated in Ontario and a growing rate of vaccine refusal among parents of school-age children.<sup>7</sup> Female vaccination rates of 80 per cent have been used in most cost-efficacy analyses,<sup>4</sup> limiting the extrapolation of any comparative cost-efficacy analyses until a time when that threshold has been definitively reached.

Interestingly, there is preliminary evidence that bivalent vaccine may possess higher immunogenicity and cross-protective efficacy for other HPV types,<sup>4,5</sup> which may confer long-term cost-efficacy. Based on cost alone (Table 1), Cervarix appears to be an attractive option, however when non-cancer outcomes (i.e., genital warts) are considered, the cost-efficacy difference is minimized.<sup>4</sup> Head-to-head clinical studies comparing the bivalent to the quadrivalent vaccine are lacking at this time, however cost and efficacy comparisons are beyond the scope of this article as currently only the quadrivalent vaccine is licensed by Health Canada for use in males.

**Table 1 Comparison of HPV vaccines available in Canada\***

	Quadrivalent vaccine	Bivalent vaccine
HPV types	6, 11, 16, 18	16, 18
Cost **	\$149.95	\$94.95
Indications	<p><b>Women 9 to 45 years</b></p> <ul style="list-style-type: none"> <li>• Genital warts</li> <li>• Cervical intraepithelial neoplasia grades 1, 2 &amp; 3</li> <li>• Cervical adenocarcinoma in situ</li> <li>• Vulvar and vaginal cancer</li> <li>• Vulvar and vaginal intraepithelial neoplasia grades 2 &amp; 3</li> </ul> <p><b>Women 9 to 26 years</b></p> <ul style="list-style-type: none"> <li>• Anal cancer</li> <li>• Anal intraepithelial neoplasia (AIN) grades 1 &amp; 2</li> </ul> <p><b>Men 9 to 26 years</b></p> <ul style="list-style-type: none"> <li>• Anal cancer</li> <li>• AIN grades 1, 2 &amp; 3</li> <li>• Genital warts</li> </ul>	<p><b>Women 9 to 45 years</b></p> <ul style="list-style-type: none"> <li>• Cervical intraepithelial neoplasia grades 1, 2 &amp; 3</li> <li>• Cervical adenocarcinoma in situ</li> </ul>
Schedule	0, 2 & 6 months	0, 1 & 6 months 0 & 6 months (ages 9 to 14)

\* As per Cervarix and Gardasil product monographs.

\*\* Average acquisition cost per dose (McKesson Canada), tendered prices unknown.

### Supporting Evidence

Substantial evidence exists to support HPV vaccination for adolescent females. Two international, randomized, placebo-controlled studies have been conducted that have included over 17, 000 women.<sup>8,9</sup> If naive to HPV infection, women experienced almost complete protection against the HPV-related outcomes under study including abnormal cytology of the vulva and cervix, anogenital warts and cervical cancer. Although the trials were relatively short in duration at only three years follow-up, and some would argue too short to make conclusions with respect to cervical cancer, there was little hesitancy to adopt a widespread vaccination program for females.

There are no studies assessing the effects of HPV immunization in males on the prevention of male to female transmission or the incidence of cervical cancer. As well, the World Health Organization (WHO) does not recommend vaccination of boys solely for the purpose of cervical cancer prevention, assuming greater than 70 per cent uptake in females. However, models show that expanding HPV vaccination programs to males would further reduce the incidence

of HPV disease and cervical cancer deaths by an additional 30 and 23 percent, respectively.<sup>11</sup>

Cervical cancer prevention notwithstanding, there are several studies showing benefits to HPV vaccination for males. A randomized, double-blind, placebo-controlled trial enrolling equal proportions of male and female children, has shown that seroconversion rates were greater than 99 per cent over the entire population with rates in boys non-inferior to those in girls.<sup>12</sup> A randomized, placebo-controlled, double-blind trial published in the New England Journal of Medicine in 2011<sup>13</sup> showed that a three-dose vaccination series with a quadrivalent HPV vaccine was 65 per cent effective in preventing genital lesions caused by HPV 6, 11, 16 or 18 in 4,056 males aged 16 to 26. In patients negative for HPV at baseline, efficacy was nearly 90 per cent.

A planned substudy of the aforementioned trial included 602 HIV-seronegative men who have sex with men (MSM) and aimed to assess vaccine efficacy in preventing AIN, a precursor for anal cancer. In the intent-to-treat population, the incidence of AIN due to HPV 6, 11, 16 or 18 declined by 50 per cent; incidence declined by 78 per cent in the

per-protocol population.<sup>14</sup> While the evidence in males is definitely less robust than for females, this landmark trial provides sufficient scientific rationale for the consideration of gender-neutral vaccination programs.

MSM have been identified as a population at increased risk of infection and adverse outcomes related to HPV,<sup>4</sup> including both anogenital warts and cancers. However, a recent study conducted at McGill University showed significant rates of oral HPV infection among heterosexual males.<sup>15</sup> More than seven per cent of men in the study had oral HPV infection, with higher rates among males who smoked, performed oral intercourse on their partner more frequently, or who had multiple partners. Prevalence was highest among males whose partner had an oral HPV infection, with rates reaching 28.6 per cent.

Not only does this study suggest that HPV may be prevalent among heterosexual males, it also suggests that transmission can occur via oral-oral and oral-genital routes. As mentioned above, HPV infection is more closely associated with oropharyngeal cancers than with penile cancers, with the former being much more common.

## It is clear that clinical evidence and medical opinion support the expansion of HPV vaccination programs to include both males and females.

Some advisory committees have recommended targeting MSM for publicly funded vaccination programs<sup>4,16</sup> as these patients are unlikely to benefit from herd immunity conferred by a female-only vaccination strategy. Models have shown favourable cost-efficacy when MSM are targeted at an age of 12 years.<sup>17</sup> However, the identification of high-risk males who are likely to engage in high-risk sexual behaviours, or even smoke, is probably not feasible before the age of 12. Young boys are unlikely to declare sexual preference before the onset of sexual maturity when vaccines are likely to confer the most benefit, further supporting a non-selective vaccination strategy for males as has already been implemented for females, regardless of risk.

Indeed, grade 8 students in Canada, the target population for some vaccination programs as discussed below, are typically 13 or 14 years of age. A survey released by the Public Health Agency of Canada in 2011 reported that by the time they had reached 14 years of age, 16 per cent of females and 18 per cent of males have had sexual intercourse.<sup>18</sup>

In major clinical trials, vaccination is overwhelmingly less

effective when participants with baseline HPV infection are included. In one trial, efficacy dropped from 98 per cent to 44 per cent.<sup>8</sup> As well, high-risk women and men, including those with multiple sexual partners and those with a history of abnormal PAP smears were typically excluded from clinical trials showing efficacy.

Most importantly, the ethical implications of withholding public funding for a vaccine that is known to reduce the burden of disease – and potentially cancer – in a specific population must be considered. While direct evidence that vaccination against HPV reduces cancer in males is lacking, the preliminary evidence is difficult to ignore. Health Canada and the Food and Drug Administration have already taken this leap of faith upon approving quadrivalent vaccine for the prevention of anal cancer in men and women, despite a lack of studies reporting hard outcomes.

### Vaccination Programs

In 2013, Prince Edward Island became the first and only Canadian province to offer the HPV vaccine to boys as part of their routine, publicly funded vaccination schedule. However, beginning in September 2014 the Alberta school immunization program includes Grade 5 boys with a four-year catch-up program for Grade 9 boys. Publicly funded immunization programs are listed by province in Table 1. The provinces vary with respect to the timing of vaccination, ranging from Grade 4 in Quebec and the Northwest Territories to Grade 8 in Ontario.

Quebec and British Columbia are notable exceptions in that these provinces offer only two doses of vaccine, compared to the other provinces, which offer three doses. This decision is based on good evidence from randomized, controlled trials and is supported by the WHO. The WHO recommends this schedule for younger women aged nine to 14 years.

However, there are fewer data, especially long-term, to support a two-dose series and a Canadian model showed cost-efficacy only if the duration of protection from the vaccine is at least 10 years and likely at least 20 years.<sup>5</sup> Data for protection are only available for approximately five to six years following vaccination, with models predicting 20 years or more of protection.<sup>19</sup> Quebec also offers, free of charge, the vaccine to immunocompromised women aged 18 to 26, including those infected with HIV, however there is no evidence for a two-dose series in this population.

As of 2014, the American Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with quadrivalent HPV vaccine for all boys in a three-dose series at age 11 or 12 years and for those aged 13 through 21 years, if not previously vaccinated. Males aged 22 through 26 years should also be vaccinated, particularly those with certain high-risk medical conditions.<sup>20</sup>

To keep things in perspective, the ACIP evidence grade and subsequent strength of recommendation, is higher for HPV vaccination in males than for other vaccine-preventable

**Table 2 HPV vaccination programs 2014**

Province / Territory	Ages	Gender
NL	Grade 6	Females
PEI	Grade 6	Females and Males
NS	Grade 7	Females
NB	Grade 7	Females
QC **	Grade 4	Females
ON	Grade 8	Females
MB	Grade 6	Females
SK	Grade 6	Females
AB	Grade 5	Females and Males
BC *	Grade 6	Females
YT	Grade 6	Females
NU	Grade 6	Females
NWT	Grade 4	Females

\* 2 doses.

\*\* 2 doses; includes immunocompromised women 18-26 years.

illnesses such as meningococcal and pneumococcal disease, for which vaccines are routinely covered for all Canadians and usually without age restriction.

Closer to home, the National Advisory Committee on Immunization (NACI) recommends the HPV vaccine for females (bivalent or quadrivalent) and males (quadrivalent) between nine and 26 years of age including MSM. In December of 2014, the committee expanded their recommendations, stating the vaccine may now be administered to males and females over 26 years of age.

The committee also expressed agreement with the WHO in that a two-dose series age at 0 and 6 to 12 months may now be considered for immunocompetent individuals 9 to 14 years of age. There is no direct evidence for a two-dose series in males, however there is no indication that the response would be any different than that observed in female studies. Immunocompromised or HIV-infected patients who receive their first dose after 15 years of age should continue to receive three doses.<sup>21</sup>

Starting in 2007, with varying degrees of catch-up programs for eligible females, Canadian provinces began offering publicly funded HPV immunization programs. As of 2010, every province in Canada had implemented a vaccine

program for school-aged girls. However, as seen in Table 2, provincial uptake of the NACI recommendations for males is lagging. Several professional organizations including the Canadian Medical Association, the Canadian Dermatology Association, the Canadian Society of Obstetricians and Gynecologists, the Canadian Cancer Society, and the Registered Nurses Association of Ontario, among others, vocally support expansion of HPV vaccination programs to males.<sup>22</sup> On a global stage, Australia, the United States and Austria have all expanded their HPV vaccination programs to include males.

### Conclusions & Recommendations

Unfortunately, public health policy with regards to HPV vaccination programs is not driven purely by scientific evidence. Public funding for vaccination against a sexually transmitted infection is subject to considerable public debate and opinion, much like other “lifestyle” illnesses such as smoking and drug abuse.

However, it is clear that clinical evidence and medical opinion support the expansion of HPV vaccination programs to include both males and females. Cost-efficacy concerns, while legitimate, are estimates at best and even female vaccination rates have been unable to meet the criteria for cost-efficacy assumed in most models. As such, the Cancer Advocacy Coalition of Canada supports the following recommendations:

- The HPV vaccine should be offered to all Canadians, regardless of province of residence, gender or sexual orientation. Specifically, the quadrivalent HPV vaccine should be offered to all males older than 9 years, with catch-up programs made available.
- Vaccination programs should target children before the age of sexual maturity, as early as nine and as late as 12 years of age, keeping in mind the duration of protection is currently not known.
- As a cost reduction measure, a two-dose series of bivalent or quadrivalent HPV vaccine may be offered to immunocompetent individuals nine to 14 years of age.
- Long-term studies assessing the efficacy of HPV vaccination in the prevention of HPV-related disease and cancers in men are warranted. Other areas of interest include estimating the duration of protection and necessity for booster doses.

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## NO EVIDENCE THAT GIRLS BECOME PROMISCUOUS AFTER THE HPV VACCINE

The concern among some families that the HPV vaccine could encourage promiscuity in their young daughters should be put to rest, according to new research from McGill published in the *Canadian Medical Association Journal*.<sup>1</sup>

The authors followed 260,493 Grade 8 girls in Ontario for an average of four and a half years - until the end of Grade 12. Half the girls had the vaccine in Grade 8 in the first two years it was offered, the other half had been in a two-year cohort just before the vaccine became available at school and did not receive the vaccine.

The study used two clinical indicators of sexual behaviour: pregnancy or a sexually transmitted infection. Checking anonymized medical records, the authors found no evidence that vaccination increased the risk of either outcome. Indeed, the authors concluded that their findings are "strong evidence that HPV vaccination does not have any significant effect on clinical indicators of sexual behaviour among adolescent girls. These results suggest that concerns over increased promiscuity following HPV vaccination are unwarranted and should not deter from vaccinating at a young age."

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