

Background information on HPV, Gardasil's HPV Vaccine, and expanding the vaccination program to include young males in BC

Human Papillomavirus (HPV) is the most common sexually transmitted infection, and an estimated 75% of sexually active people will acquire an HPV infection at some point in their lives in the absence of vaccine protection [1, 5]. More than 40 types of HPV have been identified that can infect the mouth, throat, and genital areas of both males and females [1]. The body's immune system is able to clear the infection in 90% of cases, although the immune response has been shown to be lower in males [1, 3]. If an infection persists and the immune response is insufficient, further illness can result such as genital warts and cervical, penile, anal, oral, head and/or neck cancers [1, 2, 4].

Two HPV vaccines, Cervarix® and Gardasil®, have been shown to be effective in preventing HPV infections and associated cancers in young females. Gardasil® has also been approved for young males [5]. Evidence for *cost-effectiveness* has been demonstrated for young female populations, and has therefore drawn Canadian public funding for a school-based vaccination program. The current vaccination program may not be protecting all populations experiencing high risks of HPV infection, including men who have sex with men (MSM) – who do not benefit from female-only immunity. To widen the scope and effectiveness of the HPV vaccine as well as decrease inequities that arise from a female only vaccination program it has been suggested that the program be expanded to include males as well. Inclusion of males in vaccination regimes not only has the potential to further protect unvaccinated females, but also introduces protection to MSM populations. In addition, biological interactions between HPV and HIV as well as implications of dual-infection call for further research and consideration for people living with, or experiencing risk for either or both viruses.

Although many organizations including the National Advisory Committee on Immunizations, Health Canada, and the BC Centre for Disease Control accept the efficacy and safety of both Gardasil® and Cervarix®, concerns have been raised by some regarding associated health risks, cost-efficacy, and aggressive marketing by pharmaceutical companies. The following evidence is presented to help inform the Pacific AIDS Network in their consideration of the risks and benefits of the HPV vaccine program being extended to young males.

Quick Facts

- There are more than 100 types of HPV identified, around 40 are able to infect the anogenital region [3].
- Some types of HPV are classified as low-risk and are associated with anogenital warts and mild *dysplasia* (e.g. 6 & 11), while other types (e.g. 16, 18, 31, & 45) are categorized as high-risk and are associated with high-grade dysplasia and anogenital cancers [3].
- The Gardasil® vaccine immunizes against HPV types 6, 11, 16 & 18.
- The rate of genital HPV infection in males is similar to that in females, however the immune response has been shown to be lower in males [2].
- MSM and people living with HIV are the highest risk for HPV-related diseases [6].

- HPV prevalence has been reported as upwards of 60% among all sexually active men with higher numbers for MSM, and even higher in men living with HIV [5, 7].
- More than 80% of anal cancers are related to strains of HPV covered by the Gardasil® *quadrivalent* vaccine [6].
- The association between HPV and anal and oropharyngeal cancer is comparable to the association with cervical cancer [5].
- Trends in cervical cancer have been declining while head, neck and anal cancers have been on the rise [6]. It has been estimated that by 2020 HPV will cause more oropharyngeal cancers than cervical cancer [8].
- The *prophylactic* nature of the HPV vaccine means it is most effective in a naïve population, i.e. before first sexual contact.
- The efficacy of the quadrivalent vaccine has been demonstrated in males as well as in females. NACI [2] showed an overall *per-protocol efficacy* of 90.4% in preventing HPV 6/11/16/18-related *external genital lesions*.

*See Appendices for the following summary tables.

Appendix A: Incidence of HPV-related cancer in males and females

Appendix B: Gardasil® efficacy data

Appendix C: Gardasil® safety data

Link with HIV

HPV and HIV interact in a number of ways both socially and biologically with regards to transmission, populations affected, and their influence on one another's disease progression within the body. Many people who experience risk for HIV infection also experience risk for HPV infection since both viruses can be transmitted through sexual contact. In addition each virus favours acquisition and amplification of the other virus [9].

When exposed to HIV the risk of infection has been shown to double for people infected with any type of HPV [9]. A number of biological reactions associated with HPV infection change the properties of *mucous membranes* making them more susceptible to infection, including the recruitment of T-Cells, and cellular changes allowing HIV to more readily enter cells [9]. HIV infection also has the ability to enhance HPV acquisition at the molecular and cellular levels. Immune suppression during HIV course enhances HPV infection and disease progression [9]. Co-infections often result in higher HPV viral loads, less clearance, more reoccurring latent infections, and more warts, cervical or anal dysplasia and cancer [9].

The HPV vaccine is composed of synthetic virus-like particles, not-live virus, and has proven safe for people living with HIV [9]. The antibody response was shown to be lower than in HIV-negative persons, but slightly higher in people receiving HAART [9]. Because of the added risk of acquiring HIV for those infected with HPV, there are implications of the HPV vaccine in the prevention of HIV acquisition and spread [9].

Implications for gay men and other men who have sex with men

HPV is more prevalent among gay men and other MSM than in the general population of sexually active adults [5, 7]. In addition the prevalence of anal cancer is higher in this population, especially in MSM living with HIV. Two studies have reported anal cancer prevalence MSM as 70/100,000 and 137/100,000 respectively, which are both higher than the prevalence of cervical cancer reported in any population [5, 7]. While heterosexual males are provided protection against the virus by vaccinating females, a female-only vaccination program does not directly offer protection to MSM.

One of the main arguments against adding males to the HPV vaccination program is the associated costs versus benefits. Some advocate that money would be better spent on vaccinating more cohorts of girls for the prevention of HPV spread, or programs to ramp up cervical cancer screening; however, this strategy does not reduce the over-representation of HPV and associated cancers in MSM. Most analyses of including boys in vaccination programs focus on cervical cancer rates, and do not show cost-effectiveness. When all HPV-related cancers are considered the cost-effectiveness ratios decline significantly, but are still higher than those of female-only vaccination programs [10].

Kim [11] conducted a mathematical modeling of the cost-effectiveness of targeting young MSM. Assuming coverage rates of 50% and vaccination efficacy of 90%, Kim analyzed hypothetical vaccination programs for males at 12, 20, and 26 years of age and considered protection against HPV-related anal cancer, and then both anal cancer and genital warts. The analysis showed cost-effectiveness ratios of under \$50,000 per *quality adjusted life years (QALY)* for all scenarios (See Appendix D). A key limitation in this strategy is that vaccination is most effective before sexual activity and the age at which males will identify as MSM, or at which they are willing to disclose their sexual identity to health practitioners will not necessarily be before sexual contact. Additionally stigma associated with targeting a specific sexual orientation could negatively impact this approach. Rank et al. [12] found in their study of 1169 men in Vancouver the median age between sexual debut and disclosing having male sex partners to their health care provider was 6 years, identifying the challenge with vaccination targeted to young MSM. Since the vaccine is most effective in naïve populations, before first sexual contact, vaccinating all young boys would provide the maximum amount of benefit for this population. Targeted vaccination for sexually active men having sex with men would however add additional protection for those not exposed to all 4 types covered by the vaccine [7].

While cost-effectiveness is a helpful tool in designing public health interventions, other societal factors must be considered in policy decisions – like the implications for gay men and other MSM. Despite the associated costs PEI and Alberta have chosen to expand their vaccination program to include boys [13].

In Opposition

Part of the debate around expanding the HPV vaccination program is centered around the role of pharmaceutical companies in the research surrounding safety and efficacy as well as

aggressive marketing and lobbying to vaccinate as many people as possible. Critics debate whether there has been enough research around safety and efficacy to confidently say the benefits outweigh the costs. Concerns have also been raised regarding long term efficacy and safety of the vaccine. An inquiry was launched in Japan in response to a number of reported *systemic reactions* that prompted an international symposium with a number of open debates and has resulted in the government suspending their vaccine recommendations [6, 14]. In addition serious adverse events (AEs) have been reported as convulsions, *paraesthesia*, paralysis, *Guillain-Barré syndrome*, *transverse myelitis*, *facial palsy*, chronic fatigue syndrome, *anaphylaxis*, autoimmune disorders, *deep vein thrombosis*, *pancreatitis*, and *pulmonary embolism* [15].

Data from 2006-2013 from the United States federal vaccine monitoring systems (Vaccine Adverse Event Reporting System [VAERS] and Vaccine Safety Datalink [VSD]) report on approximately 56 million vaccines given and show 21, 194 AEs; of these 92% were non-serious reactions such as fainting, dizziness, nausea, headaches, fever etc. while the other 8% were more serious events such as weakness resulting in hospitalizations or extended hospital stays, disability, or life threatening illness or death [16]. The AE data collection system is designed to record all adverse events after vaccination, and do not indicate a cause-and-effect relationship. Studies have not been able to demonstrate a causal relationship between the HPV vaccine and serious AEs but monitoring of AEs and long-term effects are ongoing [5, 6, 17].

In Conclusion

In the absence of public funding for cancer-preventing vaccine programs inevitable inequities arise, especially with differences in screening practices between high and low income settings. In this case we are discussing selective public funding based on gender. Vaccination restricted to school-aged females for the prevention of HPV has the added benefit of offering *herd immunity* to heterosexual males, however, does not offer protection to gay men and other MSM. This strategy has the potential to further increase inequities in MSM populations who are disproportionately affected by HPV and some HPV-related cancers. In addition interactions between HPV and HIV which favour one another's acquisition and amplification further increase risk of disease progression and associated cancers in MSM populations.

Although safety and efficacy data have been questioned by some research groups, the National Advisory Committee on Immunizations recommends Gardasil® to males between the ages of 9 and 26 as safe and effective for the prevention of anal *dysplasia*, anal cancer, and anogenital warts [5]. The adverse drug reactions reported through the VAERS and VSD after approximately 56 million vaccines administered are mostly restricted to non-serious events, and review of serious events have not demonstrated a causal relationship with the HPV vaccine.

Models of programs targeting vaccination of young MSM populations have shown to be cost-effective. However a number of issues reduce feasibility of this approach, including the age at which males identify as MSM, disclosure of having male sex partners to health practitioners, and stigma associated with vaccinating based on sexual-identity. Therefore, universal vaccination of all males would have the largest impact of decreasing the burden of HPV-related diseases among MSM as well as offer further protection to females and heterosexual men [12].

Glossary of Terms

Anaphylaxis: a serious and rapid allergic reaction.

Cost effectiveness: an analysis of the costs versus benefits of an intervention. Often presented in cost per quality adjusted life years (QALYs)

Deep vein thrombosis: a blockage of a blood vessel in a deep vein, most commonly in the legs.

Dysplasia: An early precursor to cancerous cells that can often be detected through screening.

External genital lesions: external genital warts, penile/perianal/perineal intraepithelial neoplasia, and penile/perianal/perineal cancer.

Facial palsy: a condition that involves paralysis of the facial nerve.

Guillain-Barré syndrome: a peripheral nervous system disorder that manifests as paralysis and weakness starting in the hands and feet.

Herd immunity: protection offered by a high number of the population being vaccinated.

Mucous membranes: the skin involved in absorption and secretion that line body cavities.

Parasthesia: tingling, pricking, numbness of the skin

Pancreatitis: inflammation of the pancreas.

Per-protocol efficacy: the efficacy calculated based only on those that fully completed the study.

Pulmonary embolism: a blockage of a blood vessel in the lung.

Prophylactic: preventative measures taken before a disease or condition is present.

Quadrivalent: having the combined power of four, in this case quadrivalent is referring to covering four types of HPV (6, 11, 16, & 18)

Quality adjusted life years (QALYs): a measure of disease burden, based on the quality and quantity of years lived attributable to an intervention. [18]. Cost-effectiveness is often presented in \$/QALY. Canada does not have a strict threshold for cost-effectiveness, however a range of \$20,000-\$100,000/QALY is estimated for Canadian health interventions [19].

Systemic reactions: a non-localized reaction involving a number of organs and tissues.

Transverse myelitis: an inflammatory condition of the spinal cord.

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Appendix A

Incidence of HPV-related cancer in males and females.

Table 1: Average annual number of cases and age-standardized incidence of HPV-associated cancers among persons aged 15 years and older in Canada (1997-2006) and estimated attributable proportion due to HPV.

Sex	Anatomical site*	Average annual incidence (per 100 000) ⁽⁴³⁾	Average annual number of cases	Estimated attributable proportion (%) ^(38, 41, 42)	
				Any HPV type	HPV types 16 and 18 (% of all HPV types)
Males	Penis	1.0	127.4	50	63
	Anus	1.6	208.2	90	92
	Oral cavity	6.5	853.1	25	89
	Oropharynx	0.64	84.3	35	89
Females	Cervix	10.1	1356.8	100	70
	Vagina and vulva	4.2	651.8	40	80
	Anus	1.7	267.0	90	92
	Oral cavity	3.3	501.2	25	89
	Oropharynx	0.18	27.2	35	89

* Anatomical site is based on the International Classification of Diseases for Oncology Third Edition (ICD-O-3) list of causes, with the exception of oral cavity which includes cancers of the “floor of the mouth”, “gum and other mouth” and “tongue”).⁽⁴³⁾

Table 1: Taken from the National Advisory Committee on Immunization’s *Update on Human Papillomavirus (HPV) Vaccines* [5].

Appendix B

Appendix B: Gardasil® efficacy data

Table 4: Efficacy of HPV4 vaccine in the Per Protocol Population against HPV-related genital infection and disease in young men 16-26 years of age (n=4065) at 2.9 years median follow-up.⁽⁸⁸⁾

Endpoint	HPV4 Gardasil® (n=1397)	Placebo† (n=1408)	Efficacy (%)	95% CI	p value
	Cases	Cases			
All external genital lesions (EGL)*	3	31	90.4 (All types) 84.3 (type 6) 90.9 (type 11) 100 (type 16) 100 (type 18)	69.2-97.9 46.5-97.0 37.7-99.8 0-100 0-100	<0.001
Condyloma	3	28	89.4	65.5-97.9	
Penile/perianal/perineal intraepithelial neoplasia (PPPIN)	0	3	100	0-100	
Persistent infection (HPV types 6, 11, 16, 18-related)**	15	101	85.6	73.4-92.9	<0.001
HPV type 6-related	4	33	88.0	66.3-96.9	
HPV type 11-related	1	15	93.4	56.8-99.8	
HPV type 16-related	9	41	78.7	55.5-90.0	
HPV type 18-related	1	25	96.0	75.6-99.9	
DNA detection†	136	241	44.7	31.5-55.6	<0.001

* EGLs include condyloma (external genital warts), penile/perianal/perineal intraepithelial neoplasia (PIN), penile/perianal/perineal cancer; case counting began after month 7

** HPV DNA detection in anogenital specimens from ≥2 consecutive visits ≥6 months apart (±1 month visit windows) or HPV type 6/11/16/18-related disease with positivity to the same type at adjacent visit

† HPV DNA detection in anogenital specimens from ≥1 visit

‡ AAHS (amorphous aluminum hydroxyphosphate sulfate) placebo

Table 2: Taken from the National Advisory Committee on Immunization's *Update on Human Papillomavirus (HPV) Vaccines* [5].

Appendix C

Gardasil® safety data

Table 13: Summary of adverse events reported among males 9 to 26 years of age (Days 1 to 15 following any dose of HPV4 Protocols 016, 018 and 020 ⁽⁹⁰⁾).

Subjects	Gardasil® (N=3002)		Placebo** (N=2219)	
	n	%	n	%
With one or more AE	2216	74	1417	64
Injection-site AEs*	1927	64	1177	53
Systemic AEs	1118	37	723	33
Vaccine-related systemic AEs	527	18	338	15
With serious AEs	9	0.3	1	0
Vaccine-related serious AEs	0	0	0	0
Deaths	0	0	0	0
Discontinued due to AE	6	0.2	4	0.2
Discontinued due to a vaccine-related AE	4	0.1	3	0.1

* All injection site adverse events are considered vaccine-related

N=number of subjects with follow-up; n=number of subjects in each category

** AAHS (amorphous aluminum hydroxyphosphate sulfate) placebo used for protocol 020 (males 16 to 26 years); saline placebo used for protocols 016 and 018 (males 9 to 15 years)

Table 3: Taken from the National Advisory Committee on Immunization's *Update on Human Papillomavirus (HPV) Vaccines* [5].

Appendix D

Cost-effectiveness of targeted vaccination of msm in Quality Adjusted Life Years (QALY).

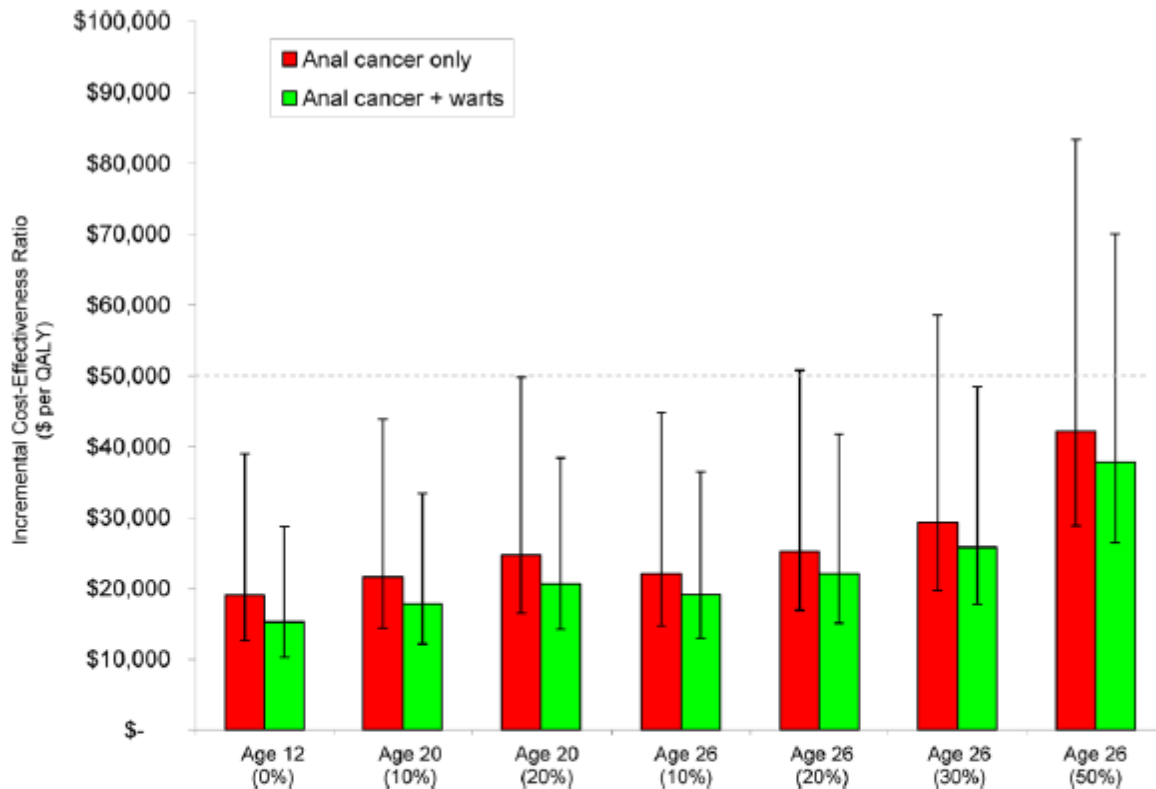


Figure 1. Impact of age at vaccination, prior exposure to vaccine-targeted HPV infections, and HIV prevalence among MSM

The graph depicts the incremental cost-effectiveness ratio (y-axis) associated with a strategy of targeted HPV vaccination of MSM, varying vaccination age and % prior exposure to vaccine-type HPV infections (x-axis). The height of each bar indicates the cost-effectiveness ratios under base case assumptions (50% coverage, 90% efficacy against vaccine-type disease outcomes, and 25% HIV positivity among MSM); the red bar represents results that include anal cancer benefits only; the green bar, anal cancer and genital warts benefits. The error bars represent results associated with varying HIV positivity among MSM (upper bar, 8% positivity; lower bar, 40% positivity). Grey dotted line denotes a cost-effectiveness threshold of \$50,000 per QALY, considered a benchmark for good value for money in the U.S.

Figure 1: Taken from Kim, 2010 [11].