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HPV Vaccination: Understanding the Impact on HPV Disease

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Background: Burden of HPV Associated Diseases

Human papillomavirus (HPV) infection is the cause of several types of cancers, genital warts, and recurrent respiratory papillomatosis. HPV is one of the most common sexually transmitted infections, with more than 70% of sexually active men and women being infected at least once in their lifetime[1-3]. Persistent infection over several years with oncogenic HPV types increases the probability of cancer development[4, 5]. HPV infection causes virtually all cervical cancers and is also associated with cancers of the anus, oropharynx, penis, vagina, and vulva[6, 7]. HPV DNA in tumor cells has been detected in some cancers of the oral cavity, esophagus, lung, prostate, and breast. However, molecular and epidemiological data demonstrating a causal relationship other than in cervical cancer are sparse[6, 8-16]. The availability of two prophylactic HPV vaccines promises to reduce the incidence and mortality of cervical cancer for women and a broader range of precancerous lesions, invasive cancers, and related conditions for both men and women[3, 17-21].

Over 40 HPV types infect the genital surface and are sexually transmitted; only about 20 types are associated with invasive cervical cancer[22]. Approximately 70% of all cervical cancers, 41% - 67% of high grade cervical lesions, and 16% - 32% of low grade cervical lesions are caused by HPV 16 and 18 – the two oncogenic, high risk HPV 'vaccine-preventable' types[3, 6]. After HPV 16 and 18, HPV 31, 33, 35, 45, 52, and 58 are the most common oncogenic types globally, and they account for an additional 20% of cervical cancers[23, 24]. Two non-

Key Points

- Human papillomavirus (HPV) is one of the most common sexually transmitted infections.
- Oncogenic, high risk HPV types 16 and 18 are associated with approximately 70% of all cervical cancers. Oncogenic HPV types 31, 33, 35, 45, 52 and 58 account for an additional 20% of cervical cancers. Infection with oncogenic HPV types is also associated with cancers of the anus, oropharynx, penis, vagina and vulva.
- Non-oncogenic, low risk HPV types 6 and 11 are responsible for 90% of anogenital warts.
- Two HPV vaccines are licensed for use in Canada, Cervarix™ (GlaxoSmithKline) and Gardasil® (Merck). While both vaccines provide protection against HPV types 16 and 18, Gardasil also protects against HPV types 6 and 11.
- Clinical trials have demonstrated both HPV vaccines to be highly efficacious (95% - 100% vaccine efficacy) against precancerous cervical lesions. However, the vaccines' long-term protectiveness is unknown at this time.
- The majority of HPV vaccine associated adverse events reported in Canada have been pain at the injection site.
- All provinces and territories in Canada have implemented publicly-funded HPV vaccination programs. However, reported HPV vaccine uptake varies across the country, ranging from around 50% in Alberta and Manitoba to approximately 85% in Newfoundland, Nova Scotia and Quebec.
- Although the HPV vaccine has the potential to play a significant role in reducing the incidence of cervical cancer, the HPV vaccine is type specific for only 70% of cervical cancers and not all girls will receive the vaccine, thus resources to maintain the availability and access to Pap tests must remain.
- Extension of the public HPV vaccination program to males is under consideration in the provinces of Prince Edward Island, New Brunswick, and Quebec.

oncogenic low risk HPV types, 6 and 11, are responsible for 90% of genital warts and most cases of recurrent respiratory papillomatosis[18, 25, 26].

The burden of HPV disease in non-cervical cancers is substantial, approximately equal between men and women. A high proportion of non-cervical HPV-related cancers occur in the oropharynx and are the 6th most common cancer worldwide[6, 27]. In Canada, more than 50% of oropharyngeal squamous cell carcinomas are HPV 16-related[28]. The natural history of these cancers and the response to treatment are different from non-HPV associated cancers of the same site. Emerging evidence in oropharyngeal cancers, particularly those of the tonsils and posterior pharynx, demonstrates that HPV positive cancers have an improved prognosis when compared with HPV negative cancers[29-32]. Due to the sexual transmission of HPV, oral sex has been identified, along with tobacco and alcohol consumption[33, 34], as a risk factor for head and neck cancers. HPV 16 and 18 are also related to cancer of the anus and the incidence of this type of cancer has increased in both men and women in the past five decades[6]. While the incidence of anal cancer is low in the general population, anal cancer incidence is high among men who have sex with men (MSM), and men and women with HIV infection[6, 35].

Anogenital warts affect approximately 1% of sexually active North Americans per year[36]. Anogenital warts, like any HPV infection, are highly contagious; 65% of people develop anogenital warts following sex with an infected partner[18]. In both men and women, the prevalence of anogenital warts is increasing, primarily due to changes in sexual behaviour[36, 37]. In Manitoba, the rate of anogenital warts has increased over a 20-year period with both incidence and prevalence being higher in men than women[17]. Overall, research confirms that anogenital warts are a burden on those who are diagnosed, and they represent a significant burden on treatment and health care budgets[37-40].

Recurrent respiratory papillomatosis (RRP) is a rare respiratory disease in both children and adults. In children, juvenile RRP affects the airways of infants and young children as a result of transmission of HPV from mother to child during birth[18, 26]. In adults, RRP may result from reactivation of a latent HPV infection or from new infection through oral sexual transmission[41]. Symptoms of RRP include hoarseness, problems with swallowing, and breathing difficulties[42]. Treatment includes repeated surgeries to remove lesions which obstruct the airway and upper respiratory tract[26]. RRP peaks among infants and young children at a mean age of 4 years and again between the ages of 20 and 30 years[18]. The prevalence of RRP is 1.7-2.6 per 100,000 children in the United States and 1.11 per 100,000 children in Canada[26, 42]. The incidence of RRP is 1.8 per 100,000 adults in the United States[43].

HPV Vaccines

Two HPV vaccines are licensed for use in Canada, Cervarix™ (GlaxoSmithKline) and Gardasil® (Merck). Cervarix and Gardasil contain non-infectious viral-like particles (VLPs) that mimic HPV viral infection[44, 45]. Virus-like particles are prepared from surface proteins of select HPV types. Because the vaccines contain no viral DNA, they cannot cause infection[44, 46-49]. Both vaccines contain HPV 16 and 18 VLPs; Gardasil also contains HPV 6 and 11 VLPs[47].

The adjuvants differ between the two vaccines. Cervarix utilizes a proprietary adjuvant containing aluminum hydroxide and 3-deacylated monophosphoryl lipid A (AS04)[47, 50]. Gardasil utilizes a standard adjuvant of amorphous aluminum hydroxyphosphate sulfate (AAHS)[48, 50]. Both vaccines are given as three separate doses over a six month period with a minimum interval of one month between the first and second dose[51]. The effectiveness of two injections of the HPV vaccine instead of three is currently being investigated[52].

Multi-centre, multi-country clinical trials have demonstrated high immunogenicity, vaccine efficacy, and safety[45, 47, 53-83] for up to five years for Gardasil[62, 81] and 7.3 years for Cervarix[55, 56, 82]. In Canada, Cervarix is licensed for the prevention of precancerous cervical lesions and cervical cancer in females between the ages of 10 and 26[49, 84]. Gardasil is licensed for the prevention of cervical cancer, vulvar and vaginal cancers, precancerous lesions, and genital warts for females between the ages of 9 and 45[48, 85, 69]. Gardasil is also licensed for the prevention of precancerous anal lesions, anal cancer, and genital warts for both males and females between the ages of 9 and 26[67].

HPV Vaccine Clinical Trials

Endpoints for HPV vaccine efficacy trials for both Cervarix and Gardasil were cervical intraepithelial lesions and adenocarcinoma in situ. These are the immediate precursors to invasive cancer and are considered ethically and biologically acceptable proxy endpoints to measure efficacy against cervical cancer[63, 86, 87]. Women with evidence of prior HPV infection were not excluded from study participation to enable generalizability of research findings. In addition to these cervical cancer clinical trials, Merck conducted clinical trials to measure vaccine efficacy against vulvar, vaginal, and anal lesions in females; penile and anal lesions in males; and genital warts in both males and females.

Clinical trials are conducted in four sequential phases[88]. Phase I clinical trials are preliminary studies of a medical intervention tested in human subjects for the first time[89]. The number of participants involved is small, usually involving 10-80 participants, and all participants receive the intervention under investigation[88]. Phase II clinical trials compare the medical intervention against no other intervention or against a current standard of care to study the efficacy of the intervention and further refine drug doses and frequencies of administration[87, 88]. These trials may not be randomized, may use control groups, and are conducted on populations of 50-200 people[88].

Phase III clinical trials randomize hundreds to thousands of participants into different treatment arms, receiving a placebo or current standard of care versus receiving the intervention under investigation[88, 89]. These trials are often double-blinded where both the participants and researchers do not know which treatment group the participant is in. Phase III clinical trials assess the effectiveness and safety of the intervention under investigation for the purpose of licensure for standard use[88, 89]. Phase IV clinical trials are conducted as post-market surveillance to determine how the intervention works in a broader mix of the general population and to gather long-term information about safety, side effects, cost-effectiveness, and sometimes new uses of the intervention[88].

Efficacy

The capacity of both HPV vaccines to prevent incident and persistent HPV 16 and 18 infections has been evaluated in terms of a variety of clinical outcomes [90, 91]. All trials of clinical efficacy were randomized and blinded. Phase II and III trials of both Cervarix and Gardasil showed 95% - 100% vaccine efficacy (VE) (see Table 1). Cervarix Phase II and III clinical trials demonstrated 95.3% - 100% VE against precancerous cervical lesions and persistent infection associated with HPV 16 and 18[47, 53-60, 81, 92]. Gardasil phase II and III clinical trials have demonstrated 95.8% - 100% VE against incident and persistent cervical, vaginal, and vulvar precancerous lesions associated with HPV 16 and 18; 90% - 100% VE against HPV 6 and 11 associated genital warts in men and women; 100% VE against penile, perianal, and perineal precancerous lesions and cancer in men; and 77.5% VE against HPV 6, 11, 16, and 18 related anal intraepithelial neoplasias and cancer in MSM[47, 61-68, 71-74, 81, 92].

Differences between clinical trials for both HPV vaccines – different adjuvants, study designs, age of participants, population inclusion and exclusion criteria related to the number of lifetime sexual partners, when case counting for analysis began, endpoints measured, assays utilized to measure outcomes, and efficacy statistical analysis conducted on the cohort of women naïve to vaccine HPV type (DNA and serology) at study enrollment[44, 81, 91] – make direct comparison of outcomes difficult.

In addition to protecting against the HPV types included in the vaccines, recent analysis of all clinical trial data has demonstrated that both HPV vaccines provided some cross-protection against non-vaccine HPV types[45, 90, 91, 93]. However, as cross-protection against non-vaccine HPV types was variable across different trials, the duration and true impact of the efficacy of such cross-protective remains unknown[93].

Immunogenicity

When administered three times over six months, both vaccines elicit an immune response substantially greater than the immune response seen after natural HPV 16 and 18 infection[46]. While immunogenicity data are encouraging, the absence of established immune measurement or antibody threshold to define correlates of protection from HPV vaccination makes it difficult to interpret or predict the clinical relevance of the data[81, 93-95]. While clinical trials report high rates of seroconversion and serum neutralizing antibodies following completion of a three-dose immunization series, duration of protection following vaccination

Table 1. HPV Vaccine Efficacy Clinical Trial Data

Vaccine	Clinical Trial	Population	Follow Up	Randomized Clinical Trial Endpoint[c]	Vaccine Efficacy[c,d]	References
Cervarix[a]	Phase II	1,113 females 15-25 years	Up to 6.4 years	CIN[e] 1-3	**95.3%** (95% CI 87.4-98.7) **to 100%** (95% CI 51.3-100.0)	53-55
	Phase III	18,644 females 15-25 years	4 years	CIN 2+, AIS[f], Cervical Cancer	**92.9%** (96% CI 79.9-98.3; p<0.0001) **to 98.1%** (96% CI 88.4-100.0; p<0.001)	57-59
	Phase II	1,040 females 20-25 years	2 years	CIN 1-3	**82.5%** (95.5% CI 59.8-93.6; p<0.0001) **to 100%** (95.5% CI 11.2-100.0; p<0.0001) CIN 1+	60
				Persistent infection	**100%** (95.5% CI 71.3-100.0; p<0.0001) Persistent infection	
Gardasil[b]	Phase II	1,158 females 16-24 years	5 years	Cervical, vulvar, and vaginal intraepithelial lesions 1-3; Cervical, vulvar, and vaginal cancer; Warts	**95.8%** (95% CI 83.8-99.5)	61,62
	Phase II/III	20,583 females 16-26 years	3 years	CIN 2+, AIS, Cervical Cancer	**99%** (95% CI 93-100)	63
	Phase II/III	18,174 females 16-26 years	Up to 6 years	Vulvar and vaginal intraepithelial lesions 2-3	**100%** (95% CI 72-100)	64
	Phase III	5,455 females 16-24 years	4 years	Cervical, vulvar, and vaginal intraepithelial lesions 1-3; Cervical, vulvar, and vaginal cancer; Warts	**100%** (95% CI 94-100)	65
	Phase III	17,622 females 16-24 years	42 months	Cervical, vulvar, and vaginal intraepithelial lesions 1-3	**96%** (95% CI 91-98) CIN 1+ **100%** (95% CI 74-100) VIN 1+ **100%** (95% CI 64-100) VaIN 1+	66
				Condyloma	**99%** (95% CI 96-100) condyloma	
	Phase III	4,065 males 16-26 years	36 months	External genital lesions	**90%** (95% CI 69-98) External genital lesions	47, 67, 68
				Penile, perianal, and perineal intraepithelial lesions (PIN) and cancer	**100%** (95% CI <0-100) PIN1+	
	Phase III	3,819 females 24-45 years	4 years	Persistent infection, cervical lesions 1-3, external genital lesions (condyloma, vaginal and vulvar lesions 2-3)	**88.7%** (95% CI 78-95) Combined	69,70
	Phase III	598 MSM 16-26 years	2.5 years	Anal intraepithelial neoplasias 1-3and cancer	**77.5%** (95% CI 39.6-93.3)	67, 71-74
				High grade anal intraepithelial lesions 2+	**74.9%** (95% CI 8.8-95.4)	

a. HPV vaccine types 16 and 18 associated disease.

b. HPV vaccine types 16, 18, 6, and 11.

c. Vaccine efficacy for incident and persistent infection related to HPV vaccine types.

d. According to protocol/per protocol population statistical analysis reflecting participants who were HPV vaccine type seronegative and DNA negative at enrollment and one month following completion of three dose vaccination, and received all three vaccine doses within the prescribed schedule.

e. CIN – cervical intraepithelial lesion.

f. AIS – adenocarcinoma in situ.

will be known only through long-term surveillance of breakthrough disease[81, 93, 95]. Long-term vaccine efficacy is an important unknown factor in determining the need for booster immunization, specifically since immunization is recommended prior to sexual debut and waning protection may not be apparent for many years[81].

Safety

The majority of adverse events reported in Canada have been pain at the injection site which is consistent with clinical trial research findings[2]. Additionally, 22 hospitalizations, and one death have been reported; however, there has been no direct link to the vaccine as the cause of death[2, 96]. Australia reported seven allergic responses with no serious after effects out of 269,680 Gardasil doses administered in 2007, a rate of 2.6 per 100,000 doses[97]. In the United States, of 7 million Gardasil doses administered in 2007, 2,531 adverse events were reported. This translates to a rate close to 0.1 per 100,000[96, 98], which falls well below the World Health Organization categorization of "very rare" occurrences (<1 in 10,000)[97-99].

HPV Vaccination Programs by Province

All provinces and territories have implemented publicly-funded HPV vaccination programs with the goal to reduce cervical cancer risk[2]. At least one school-grade cohort of females in each province and territory has access to a public-funded school-based HPV vaccine program. Some provinces offer vaccination to a larger population of young women outside the school-based programs[100, 101]. Reported HPV vaccine uptake varies widely across the country, ranging from approximately 50% in Alberta and Manitoba to 85% - 86% in Newfoundland, Nova Scotia, and Quebec. Table 2 presents available HPV vaccine program data and coverage rates by province[100, 101] (personal communications with Dr. E. Kliewer, Epidemiologist, CancerCare Manitoba, April 29, 2010, and Dr. M. Steben, Medical Consultant, Institut national de santé publique du Québec, July 25, 2011).

In addition to the regular HPV vaccination schedule of three doses in six months, Quebec has implemented an extended three-dose vaccination schedule for females in the fourth grade school vaccination program; the first two doses given in grade four with the third dose provided in grade nine[102]. The Quebec Government has speculated that the extended vaccination strategy would provide comparable protection to the recommended three dose in six month schedule, with the delayed third dose in grade nine offering optimal protection following the onset of sexual activity[102] (personal communication with Dr. M. Steben, May 11, 2011).

Quebec offers the most comprehensive HPV vaccination program while Manitoba, Nova Scotia, Nunavut, Ontario, and Prince Edward Island offer the program to only a single year cohort. There is no relationship between the incidence of cervical cancer and the HPV vaccination programs offered in each province and territory[103]. Limitations in data sharing agreements and HPV vaccine program evaluation infrastructure have impeded vaccine coverage reporting in some jurisdictions[101].

Impact of HPV Vaccination on Cervical Cancer Screening

Screening by means of the Pap test (to detect premalignant and malignant processes in the ectocervix) has significantly reduced the incidence and mortality of cervical cancer in the last 30 years[104]. Despite the demonstrated effectiveness of Pap tests as a secondary prevention strategy, large portions of the population are not tested on a regular basis[104]. The development of cervical cancer from initial HPV infection to precancerous lesions and cancer takes 10 to 20 years and 90% of women with a precancerous cervical lesion will not develop invasive cervical cancer as the majority of low grade lesions resolve on their own[5, 105, 106]. The long duration between infection and development of high grade lesions allows Pap test screening to identify abnormal changes on the cervix and to prompt the initiation of early treatments[104, 107]. However, at least 60% of women diagnosed with invasive cervical cancer have an inadequate Pap test screening history or no evidence of previous Pap tests[104, 107]. HPV vaccination, as a primary prevention strategy, has the potential to play a significant role in the reduction of cervical cancer incidence by reaching females prior to sexual debut and exposure to HPV[108, 109]. The HPV vaccine is type specific for only 70% of cervical cancers and not all girls will receive the vaccine, thus resources to maintain the current secondary prevention strategies of Pap tests for cervical screening must remain[97, 109, 110].

Table 2. Vaccination Program by Province[100, 101]

Province	Year Started	Vaccine Population (Female)	Coverage (%)
Alberta	2008	Grade 5 Catch up Grade 9 2009 to 2012	50-60[a,b]
British Columbia	2008	Grade 6, 9	62[a]
Manitoba	2008	Grade 6	52-61[a,b]
New Brunswick	2008	Grade 7 Catch up Grade 8 for 2008-2009	-
Newfoundland	2007	Grade 6, 9	85[a,b]
North West Territories	2009	Grade 4 Catch up Grade 9-12 2009-2014	-
Nova Scotia	2007	Grade 7	85[a,b]
Nunavut	2009	Grade 6	-
Ontario	2007	Grade 8	53[a]
Prince Edward Island	2007	Grade 6	85[a,b]
Quebec	2008	9-17 year olds extended until summer 2012 With school based program Grade 4 and Grade 9 Catch up for all women needing coverage (9-17 year olds)	81-86[a,b,c]
Saskatchewan	2008	Grade 6 Catch up Grade 7 for 2008-09	58-66[a,b]
Yukon	2009	Grade 6 Catch up Grade 7, 8	-

a. HPV immunization coverage for first year of program (3 doses).
b. HPV immunization coverage for second year of program (3 doses).
c. 2 and 3 dose HPV immunization coverage.
- Information not available.

The populations at highest risk for cervical cancer are still 'hard to reach' with both current screening technology and vaccination programs[111, 112]. Bridging primary and secondary prevention strategies is imperative to reduce the burden of HPV disease[110, 113]. These include determining the dynamics between vaccination and ongoing screening programs, extending the intervals between screening tests, and strategies for sustaining and improving vaccination and screening rates in low resource settings[109, 112, 114, 115]. Additional issues are the logistical barriers for successful uptake of a three dose vaccine in young populations, the ongoing issue of targeting hard-to-reach populations, and the inclusion of males in vaccination programs[3, 110, 113, 115].

The complementary roles of primary prevention through HPV vaccination and secondary prevention through cervical cancer screening rely on high population uptake of both interventions. Modeling studies on the impact of HPV vaccine on cervical cancer rates estimate that when 90% of the populations of young women are vaccinated prior to

sexual activity, there will be a 91% decrease in HPV type 16 cervical cancer incidence alone[116]. Since 16% - 32% of low grade and 41% - 67% of high grade abnormalities[3, 6] are positive for HPV 16 and 18, it has been suggested that the vaccine will permit less aggressive management of these abnormalities and thus impact future health care costs[109]. Current data on the distribution of HPV types among women aged 18-23 enrolled in vaccine clinical trials do not support initiation of cervical cancer screening at a younger age or a change to screening intervals for women[117]. Modeling studies to determine the impact of vaccination on future screening practices and cervical cancer incidence suggest that vaccination is unlikely to lead to increases in cervical cancer incidence as a result of decreased cervical cancer screening[118].

Impact of Vaccination on HPV Disease

Australia is the first jurisdiction to report a strong correlation between HPV vaccination with Gardasil (HPV 16, 18, 6, 11) and a decrease in HPV-associated diseases[119, 120, 121]. A significant decline in the number of cases of genital warts from 11.7% in 2004 to 2007 to 4.8% in 2007 to 2009 (59%, 95% CI 54-61; *p*trend<0.0001) in women 26 years of age and younger was demonstrated after the introduction of the HPV vaccine[120]. During the two-year study period, the authors also found a significant decline of genital warts from 17.3% to 10.5% (39%, 95% CI 33-46; *p*trend <0.0001) in the population of heterosexual men between the ages of 12 and 26[120]. The authors concluded that a reduction of HPV 6 and 11 associated diseases in the cohort of vaccinated females reduced exposure of the young male population to these HPV types[120, 121].

Another study in Australia assessed the impact of HPV vaccination on the incidence of cervical abnormalities three years following vaccination[122]. Following the introduction of the quadrivalent vaccine to all women between the ages of 12 and 26, a decrease of 0.38% (95% CI 0.61-0.16) in the incidence of cervical abnormalities, CIN 2 or worse and adenocarcinoma in situ, was found in females younger than 18.

A recent modeling study utilized HPV infection as the endpoint for the evaluation of vaccine impact rather than precancer or cancer disease. Vaccinating 12-year-old girls projects a reduction in HPV 16 prevalence by 61%, HPV 18 prevalence by 92%, and HPV 6/11 prevalence by 100% 50 years after the start of vaccination[123]. The model assumptions include at least 70% vaccine coverage rates, 99% vaccine efficacy, and vaccine protection of 20 years.

Vaccinating Males

HPV infection is an important concern for both disease burden among men[124] and the risk of transmission to women[3]. Oncogenic HPV is strongly associated with cancers and high-grade dysplasias of the anogenital tract including the anus and penis, and is also associated with a proportion of oropharyngeal cancers. The sexual behaviour of males and their role in HPV transmission to women contributes to the disease burden in females[124, 125]. In addition, the herd immunity anticipated for heterosexual men from “female-only” vaccination programs exclude protection in MSM populations[35, 126]. Risk factors for HPV infection among men have been identified as the number of lifetime sexual partners and immune status, specifically related to HIV status. Circumcision has also been shown to be protective by reducing HPV sexual transmission and penile infection[7, 125, 127-133].

In Canada, anogenital warts are a significant burden of illness and represent significant costs to the healthcare system[134]. In Manitoba between 1984 and 2004, the incidence of anogenital warts was higher in men than women; prevalence in 2004 was 165.2/100,000 for men and 128.4/100,000 for women[17]. In British Columbia between 1999 and 2006, the overall incidence of anogenital warts was also higher for men than women; 1.31 per 1,000 in men and 1.21 per 1,000 in women [40].

Globally, the incidence of HPV disease among MSM is increasing rapidly[35, 127, 135]. It has been estimated that up to 95% of MSM who are HIV-positive also carry anal HPV infection and their risk of anal cancer is significantly higher than the general population[127, 136, 137]. In an international, multi-centre HPV vaccine clinical study, prevalence of HPV infection was higher in MSM than heterosexual men; 30% of MSM were infected with HPV 6, 11, 16 or 18 compared with 8% of heterosexual men at enrollment[127].

Modeling of strategies to vaccinate 12-year-old boys projects reduction of HPV 16 infection by 88% - 94% in females and 68% - 82% in males by 2050[125]. Vaccinating males is also suggested to reduce male

HPV-related cancers by 22% - 27%. Consequently, modeling studies which include males in an HPV vaccination program demonstrate health and economic benefits over and above those observed from current "female-only" programs[125, 138, 139].

Debates have arisen regarding the benefits to population health in expanding HPV vaccination to young men. On the one hand, if efforts to vaccinate 100% of all young women were achieved, this would provide herd immunity (the minimum threshold of immunity at the population level needed to interrupt the transmission of an infectious disease and to protect the entire population) and translate to reduced HPV disease in men as well[3]. However, this outcome has not been demonstrated and high levels of vaccine uptake have not yet been achieved[3, 140]. The degree of herd immunity and protection from HPV transmission among males and females are dependent on the proportion of females vaccinated in a population[3]. In addition, as noted above, protection does not extend to MSM populations[35, 126]. On the other hand, vaccinating both young men and women may also provide herd immunity, reducing the transmission of HPV from men to women[3]. While this transmission reduction theory has also not been tested, vaccinating males may also reduce the burden of HPV disease among MSM[3, 140] and may improve overall HPV vaccine uptake through gender neutral immunization and education strategies[141].

Gardasil is efficacious against infection by HPV 16, 18, 6, and 11 types in boys and men between 16 and 26 years of age (90.4% VE; 95% CI 69.2-98.1)[47, 67, 68, 77]. HPV vaccine efficacy in preventing genital lesions was demonstrated to be 92.4% among heterosexual males and 79.0% among MSM [68]. HPV vaccine efficacy in preventing any grade of anal intraepithelial neoplasias in a subpopulation of MSM was 77.5% (95% CI 39.6-93.3) [67, 71-74, 142]. HPV vaccination has the potential to significantly reduce HPV associated anogenital infection and disease, and benefits could be maximized by vaccinating boys before they become sexually active[68, 129, 143]. Vaccinating males could enhance herd immunity among women, impact HPV associated anogenital and oral disease burden in both heterosexual and MSM populations, and address health equity issues in the prevention of HPV diseases in the population[35, 135, 144, 145].

Gaps in Research and Practice

Pre-adolescent vaccination of girls is consistently found to be attractive in the context of current screening practices, provided there is complete and lifelong vaccine protection and widespread vaccination coverage[146]. Vaccinating females prior to initiation of sexual activity is expected to result in significant decreases in cervical cancer incidence rates and health care costs[50, 147-155]. Modeling studies using current vaccine efficacy data, vaccine costs, and cervical cancer screening rates have demonstrated current HPV vaccination utility and cost-effectiveness[143]. Cost-effectiveness studies utilizing the same modeling criteria have not demonstrated health benefits for vaccinating women over the age of 30 who subsequently continue routine screening or for vaccinating males[148]. However, female-only vaccination strategies are being challenged and their limitations highlighted as the broader burden of HPV-associated diseases becomes recognized. Estimates of the impact of vaccinating boys could change if prevention of diseases other than cervical cancer is also included in research and modeling studies[138, 140, 152]. To better understand and evaluate the potential impact of HPV vaccination in the population, better data on incidence, prevalence, and impact of male and female HPV-associated diseases and cancers are needed to revise current cost-benefit models [146, 156].

In terms of vaccinating males, cost-effectiveness is dependent on vaccine coverage of females. The most favorable scenario for male vaccination is when coverage of females is low[143, 156]. Males are not currently included in the publicly-funded HPV immunization programs in Canada. Economic models for cervical cancer prevention indicate that if vaccine coverage is high in girls, including boys in a vaccination program will not be cost-effective as herd immunity will eventually occur[156]. However, there is a high level of uncertainty with this prediction, and it is questionable whether herd immunity would extend to MSM and gay populations. Also, the rationale for immunizing males is strengthened when enhanced protection against HPV infection and disease in females could be achieved.

Recent statements from health jurisdictions and medical associations have encouraged the inclusion of males in HPV vaccine programs. The Federation of

Medical Women of Canada (FMWC) "encourages all provinces and territories to include males in the school-based prophylactic HPV vaccination programs as an essential step in the prevention of HPV infection and its related diseases"[157]. Extension of the public program to males is under consideration in the provinces of Prince Edward Island,[158] New Brunswick,[159] and Quebec (personal communication with Dr. M. Steben, July 25, 2011).

A wide range of issues remain to be considered in terms of HPV research gaps and policy decisions regarding future HPV vaccination strategies. There are now two licensed HPV vaccines in Canada. Consideration of vaccine preference for public programs and private purchases, management of vaccine interchangeability, surveillance outcomes, and long-term vaccine effectiveness will be required for national guideline development[160]. Further research is needed to investigate the use of quadrivalent HPV vaccines in males to determine vaccine and health outcome cost-effectiveness and to evaluate the issues of vaccination equity related to expanded vaccine uptake strategies targeting high risk and hard-to-reach populations[138, 139,146,160].

Conclusion

Canada has the human capital, expertise, and infrastructure to conduct HPV research[160]. Research funding is required for basic science research and epidemiological studies with committed operating funds for primary prevention evaluation and surveillance infrastructure strategies[160-166]. Given the large disease burden of HPV in both genders, HPV disease transmission, natural history, vaccination, and research should be considered from a population perspective, and health policies should be reviewed and revised accordingly[135, 163-167]. The HPV vaccine has the potential to significantly reduce the incidence of anal, cervical, oral, vaginal, and vulvar precancerous lesions and cancer as well as genital warts in both males and females. With HPV vaccine approval to prevent four types of cancer and their precursor lesions associated with HPV 16 and 18 and genital warts associated with HPV 6 and 11, policy makers are challenged to consider increasing access to publicly-funded HPV vaccine programs by both males and females, and females of broader age cohorts as a preventative health strategy to reduce HPV diseases.

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