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Abstract

Human papillomavirus (HPV) remains the most common sexually transmitted infection with a lifetime incidence of over 75%. Based on US data from the Centers for Disease Control and Prevention (CDC), 64% of invasive HPV-associated cancers are attributable to HPV 16 or 18 (65% for females; 63% males) and may be prevented by vaccination with either the quadrivalent or nonavalent HPV vaccine. Public HPV vaccination programs are now the norm for women aged 9–45 years and men aged 9–26 years in Canada. Yet, only recently have guidelines begun to consider vaccination of men older than 26 years of age. There now exist compelling reasons to recommend vaccination against HPV amongst males >26 years of age. Recognizing that the risks posed by HPV infection persist beyond 26 years of age, that the vaccination of men aged 26–45 years with HPV vaccine confers immunogenicity at levels demonstrably efficacious against HPV-related diseases, and that the Food and Drug Administration recently expanded the HPV vaccination to include older men, it is argued that HPV vaccination in men older than 26 years of age should be routinely recommended.

Keywords

human papilloma virus, vaccination, guidelines, >26 years of age, cancer, malignancy, prevention, males

Introduction

Human papillomavirus (HPV) remains the most common sexually transmitted infection with a lifetime incidence estimated at over 75%.¹ Amongst both men and women, HPV causes mucocutaneous warts, intraepithelial neoplasia, and malignancy. Currently, public vaccination programs across Canada include HPV vaccination for young men and women; such a practice is rapidly becoming the norm internationally.^{2–4} However, in Canada and elsewhere, HPV vaccines are only indicated for women aged 9–45 years and men aged 9–26 years, and guidelines regarding HPV vaccination of men >26 years of age remain poorly established.⁵ A summary of vaccination recommendations for select countries is presented in Table 1. The most recent recommendation from the Canadian National Advisory Committee on Immunization (NACI) in 2016 states that HPV vaccines “*may* be used in males over 26 years of age who have not been vaccinated previously or who have not completed the series” whereas Health Canada’s Immunization Guide states that the HPV vaccine may be administered where there is an *ongoing risk* of exposure to HPV.⁶ However, recent Food and Drug Administration (FDA) approval of the nonavalent HPV

vaccine for men aged 27–45 years in October 2018 suggests the need for re-examination of these policies.⁷

Despite the paucity of literature supporting the vaccination of men >26 years of age, there exists sufficient data to warrant updating current Canadian guidelines recommending vaccination in this subgroup.

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Table 1. Summary of Select Available National HPV Vaccination Guidelines.

Jurisdiction		Older men	Other groups
Canada: National Advisory Committee on Immunization ⁶	Recommended	No recommendation	Women 9-26 Men 9-26
	May vaccinate	Men over 26 who have <ul style="list-style-type: none"> not been vaccinated previously not completed the series 	Women over 26 who have <ul style="list-style-type: none"> not been vaccinated previously not completed the series Immunocompromised individuals Immunocompetent HIV infected individuals
Australia: Department of Health ⁵⁸	Recommended	Men who have sex with men	Men 9-18 Women 9-18 immunocompromising conditions
	Not routinely recommended but may benefit	Men 19 and greater	Women 19 and greater
New Zealand: Ministry of Health ⁵⁹	Recommended	Men who have sex with men Men 27 and older who have <ul style="list-style-type: none"> had little previous exposure to HPV and are now likely to be exposed 	Children 14 and under (no stated minimum) Men 15-26 Women 15-26 Transplant patients 9-26 Post-chemo patients 9-26 Women 27 and older who <ul style="list-style-type: none"> have had little previous exposure to HPV and are now likely to be exposed
	May vaccination/not routinely recommended	No recommendation	Individuals infected with HIV No recommendation
Europe: European Center for disease control and Prevention ^{3,60,61}	Recommended	Austria: Men up to 60 Liechtenstein: Men up to 30 Other EU states: not recommended	Variability between EU states
	Not routinely recommended	Variability between EU states	Variability between EU states
United States: Center for Disease Control: Advisory Committee on Immunization Practices ^{11,57}	Recommended	Men who have sex with men	Women 9-26 Men 9-21 Immunocompromised individuals
	May be vaccinated	No recommendation	Men 22-26

EU, European Union; HIV, human immunodeficiency virus; HPV, human papilloma virus.

Current Male-Indicated HPV Vaccines

Vaccines

Two vaccines against HPV are currently approved for men in Canada: the quadrivalent vaccine and the nonavalent HPV vaccine. While as the quadrivalent vaccine, covering HPV types 6/11/16/18, was initially approved in 2006 for use in women aged 9-26, it was only indicated for males aged 9-26 as of February 2010.^{5,8,9} In January 2012, the NACI published its recommendation for routine HPV vaccination of males and females aged 9-26 years; pan-Canadian

immunization programs were instituted by the summer 2017.^{2,9} In 2015, the nonavalent vaccine, covering additional HPV strains 31/33/45/52/58, was approved for use in women aged 9-45 and men aged 9-26 years.¹⁰

The majority of HPV-related diseases may be prevented through the administration of HPV vaccines. Based on the study by the Centers for Disease Control and Prevention (CDC) in 2015, 64% of invasive HPV-associated cancers are attributable to HPV 16 or 18 (65% for females; 63% males) and may be prevented by vaccination with either the quadrivalent or nonavalent vaccine. The additional strains covered

by the nonavalent vaccine, 31/33/45/52/58, are thought to cover an added 10% of HPV-related cancers.¹¹

Burden of HPV Infection and Disease in Men

HPV is a double-stranded DNA virus and more than 200 HPV strains are thought to exist.¹² The virus is most often transmitted sexually by epithelial–epithelial contact.¹³ The majority of HPV infections are asymptomatic but can cause mucocutaneous warts, intraepithelial neoplasia, and squamous cell carcinoma (SCC) of the penis, anus, and oropharynx, as well as oral and laryngeal cancers.¹⁴

Whereas the rate of novel HPV infections decreases with age in women, rates of new HPV infection are constant in men as they age.^{15,16} One explanation lies in differences in immunogenicity between men and women; recent research has demonstrated that following HPV infection, men are 4–10 times less likely to seroconvert than women.¹⁶ It has also been demonstrated that even when men do seroconvert, circulating antibodies do not confer any protection against reinfection with HPV, in contrast to women where they confer partial immunity.¹⁷ The fact that men acquire *de novo* HPV infections at a steady rate throughout life suggests an increased need for vaccination amongst older men.

Anogenital Warts

Over 90% of anogenital warts are caused by low-grade HPV types 6 and 11.¹⁸ Few studies have considered the epidemiology of HPV infection in Canada; those that did likely underestimated rates of HPV as it is not a reportable disease, and diagnostics for HPV are neither widely available nor publicly funded.^{9,19} Nonetheless, the incidence of anogenital warts in Canada remains slightly higher in men than in women at 154 versus 120 per 100 000 persons.^{20,21} The prevalence of anogenital warts remains highest amongst immunocompromised patients and men who have sex with men (MSM), particularly those that are HIV positive.^{22,23} However, both Canadian and American studies demonstrate a peak incidence arising later in life amongst men (peaking between 25 and 44 years) as compared with women (peaking between 20 and 34 years of age).^{20,24} The median time to clearance of HPV 6 and 11 infections is under 1 year.¹⁵ Thus, in men, many infections causing genital warts are acquired after 26 years of age and could be prevented through vaccination.

The long-term psychosocial impact of HPV infection may be marked; men with genital warts have higher rates of sexual dysfunction, depression, anxiety, and demonstrate a reduction in quality of life adjusted years.^{18,25,26} Perhaps in part due to the anxiety they elicit, genital warts prompt many physicians, and specifically, dermatological consultations.²⁷ Treatment of genital warts consumes vast medical

Table 2. HPV-Associated Cancer Prevalence Between 1993 and 2005 Based on Seven US Population-Based Cancer Registries.¹⁴

Cancer tissue site	% positive for HPV	% Positive for high-grade HPV types 16 and 18
Anus	91.1%	79.4%
Oropharynx	70.1%	60.2%
Penis	63.3%	47.9%
Oral	32.0%	32.2%
Laryngeal	20.9%	7.5%

resources—£58.5 million (\$102 million CAD) annually in the United Kingdom.²⁸ Interestingly, one British group posited that the benefits of a universal vaccination program would outweigh the costs related to anogenital warts alone.²⁸

HPV-Associated Cancer

Persistent infection with high-grade HPV strains precedes the development of high-grade squamous intraepithelial neoplasia.²⁹ The latency time of persistent HPV infection to invasive malignancy may be up to several decades.^{29–32}

In a recent study by the CDC, HPV types 16 and 18 were detected in a significant proportion of SCCs affecting men, including the majority of anal, oropharyngeal, and penile cancers as presented in Table 2.^{14,33} Despite the introduction of HPV vaccination programs, rates of SCC across all sites have been either steadily increasing or stable.^{23,34–38} Of note, not only has the overall rate of oropharyngeal cancer been rising across Canada but the proportion of HPV 16+ cancers has recently jumped from 47% in 2000 to 74% in 2012.^{34,37} Oropharyngeal SCC, which mainly affects men, has now surpassed cervical cancer as the most common HPV-associated cancer.³⁵ Overall, the most recent estimates of HPV-associated cancer incidence was reported at 3.8 cases per 100 000 per year in Canada and 7 cases per 100 000 per year in the United States.^{7,38}

MSM and, most importantly, MSM who are infected with HIV (MSM + HIV) are known to have higher infection rates of HPV and higher incidence of HPV-related cancers.³⁹ The prevalence of HPV 6, 11, 16, and 18 was noted in 30% of MSM vs only 8% of heterosexual males.^{40,41} Palefsky et al (2005) noted that 95% of MSM + HIV carry HPV infection, 52% having anal intraepithelial neoplasia (AIN), a 37-fold higher risk of anal cancer as compared with the general population.⁴²

An elevated incidence of HPV-associated cancers amongst solid organ transplant recipients has also been observed. It is theorized that this is due to the use of specific immunocompromising medications. Amongst men, significant increases in anal and penile cancer rates following a solid organ transplant were observed, with standardized incidence

ratios of 11.6 and 18.6 cases per 100 000 men per year, respectively.⁴³

Presumed efficacy of vaccines in men >26 years. HPV vaccines have demonstrated efficacy against anogenital warts and AIN amongst men 16-26 years of age.⁴⁴⁻⁴⁶ A randomized trial of the quadrivalent vaccine (HPV types 6/11/16/18) amongst men aged 16-26 years demonstrated 90.4% (95% CI: 69.2-98.1) efficacy against genital warts and a reduction of persistent HPV infection, between 78% for HPV-16 (95% CI: 55.5-90.9) and 96% for HPV-18 (95% CI: 75.6-99.9).⁴⁴ A subpopulation analysis of MSM members also showed efficacy of 77.5% against HPV-6/11/16/18-related AIN.⁴⁵ Yet, to date, studies have not explored vaccine efficacy at other anatomical sites or for men older than 26 years of age. The lack of research amongst men >26 years of age is in stark contrast with studies demonstrating long-term efficacy of HPV vaccine amongst women aged 27-45 years.⁴⁷

However, recent studies concerning immunogenicity of the quadrivalent vaccine amongst men 27-45 years suggest that vaccination is likely efficacious. The Mid-Adult-Aged Men (MAM) study evaluated immunogenicity following vaccination of 150 men 27-45 years with the recommended 3-dose schedule of the quadrivalent vaccine.⁴⁸ The study revealed that 100% of vaccinated men seroconverted, expressing mean geometric titers of anti-HPV 6/11/16/18 IgG comparable to those observed in men aged 16-26 years, where efficacy against HPV-associated disease is proven. Wilkin et al (2010) also demonstrated immunogenicity of quadrivalent vaccine amongst men with HIV aged 22-61 years; seroconversion in excess of 95% was observed for all 4 subtypes.⁴⁹ Indeed the FDA's decision to expand the indications of the nonavalent vaccine to include men aged 27-45 years was indeed based on the findings of the MAM study.⁵⁰

In terms of safety, neither the MAM study nor the work by Wilkin et al reported any incidence of serious adverse events following vaccination. The MAM study also reported that the number of mild to moderate reactions in response to HPV vaccines was lower than that reported amongst females aged 26-45 years.^{48,51}

Lower vaccination rates amongst Canadian men. The delay in the implementation of public vaccination programs for men and lower vaccination rates amongst men suggests that the majority of men >26 years of age remain unprotected against HPV. The first public Canadian HPV vaccination program was implemented in 2007 for school-aged females; by 2010, programs for girls had been implemented in all provinces and territories. However, the first public vaccination program for males began in 2012, with national coverage only being achieved in the summer of 2017.¹⁹ This delay in the implementation of male vaccination programs implies lower vaccination rates amongst males. For instance, in Alberta, prior to the implementation of a public program for male

vaccination, 98.3% of those vaccinated against HPV were female.⁵²

Despite the implementation of gender-neutral vaccination programs in Canada, a gap remains between the vaccination rates of men and women. A 2015 study from Prince-Edward Island demonstrated that the grade 6 girls were 1.5 times more likely than boys to have been fully vaccinated against HPV.⁵³ Similarly, in Ontario, over the 2016-2017 school year, 59.4% of girls aged 12 years received HPV vaccines vs only 53.4% of boys aged 12 years.⁵⁴ Thus, not only were male vaccination programs implemented nearly a decade later than for females but lower rates of male vaccination persist despite gender-neutral vaccination programs; nearly half of eligible men go unvaccinated.

Future directions: HPV vaccine for the treatment of persistent HPV infection. Recent research suggests that HPV vaccination may have therapeutic efficacy against pre-existing HPV-related diseases. Several case reports have demonstrated effectively treating recalcitrant common warts (HPV strains 1, 2, 3, and 4) with HPV vaccination in immunosuppressed patients.^{55,56} It is hypothesized that the HPV vaccine exerted an effect by means of cross-protection owing to common HPV capsid epitopes and homology between vaccine-directed strains and other HPV types.^{55,56} The subject of future research, the prospect of treating HPV-related disease with the vaccine is exciting, especially amongst older men harboring significant disease.

Conclusions and Recommendations

Current evidence indicates that protection afforded by an HPV vaccination would be beneficial for men aged 27-45 years, especially considering that men contract HPV at a constant rate throughout their lifetimes.^{15,16} While the relative proportion of HPV infections acquired beyond 26 years of age has yet to be elucidated, rates of HPV-related disease continue to rise amongst Canadian men.^{23,34-38} Furthermore, evidence suggests that the majority of HPV infections causing anogenital warts are acquired after 26 years of age.^{15,20,21} As men continue to acquire new HPV infections past 26 years of age, HPV vaccination for these individuals should be recommended.

HPV vaccination should be recommended to men aged 27-45 years as it is safe and demonstrates immunogenicity at levels proven to generate efficacy.^{6,11,48-51} Various studies and national health authorities have made the inference that vaccination is almost certainly efficacious against HPV-related illness on the basis of immunogenicity data alone.^{11,14,48,50,57} As per the director of the FDA's Center for Biologics Evaluation and Research, expansion of vaccine indications to men 27-45 years of age "represents an important opportunity to help prevent HPV-related diseases in a broader age range".⁸

A large proportion of men would benefit from vaccination later in life since many do not participate in a pan-Canadian vaccination programs in youth.^{53,54} The delayed creation of public vaccination programs for males, as well as lower vaccination rates of males following their implementation, means that many, if not the majority, of Canadian men >26 years of age remain unvaccinated against HPV.^{19,52-54}

We recommend that HPV vaccination guidelines be immediately amended to recommend routine vaccination of men aged 27-45 years.

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