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HPV Vaccination in Men: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Context and Policy Issues

Human papillomaviruses (HPV) are double-stranded DNA viruses that infect the skin and the mucosa of the anogenital and digestive tracts; more than 100 HPV genotypes have been identified.[1] The 30 to 40 genotypes that infect the anogenital tract fall into two groups: the low-risk viruses such as HPV 6 and11 that cause genital warts in men and women, and the high-risk viruses (principally HPV 16 and18) that cause anogenital and oropharyngeal cancers in men and women.[1] HPV is the most common viral infection of the reproductive tract.[2] It is responsible for approximately 5% of the global cancer disease burden.[1,3]

The probability of a sexually active man or woman acquiring a new genital HPV infection each year is 0.29–0.39 per 1000 person-months; however, unlike women, the rate of acquisition in men remains constant with increasing age so an older median age at diagnosis of HPV-related cancers is observed in men.[4] Antibodies to natural infection do not appear to provide protection against subsequent HPV infection in men, while partial protection is noted among women, thus explaining an overall higher prevalence of HPV infections in men as well as a sustained incidence and prevalence of HPV infection at multiple anatomic sites (anal, genital, oral) across the lifespan of men.[4] This may be due to may be differences in the immune response to natural HPV infection between the sexes.[4]

Within the past decade or so, several HPV vaccines have become available. Approved by Health Canada in July 2006, the original 4-valent (4V) vaccine, Gardasil, protects against four types of HPV (6, 11, 16, and 18) that cause 70% of cervical cancers, 90% of genital warts, and 80% to 90% of anal cancers.[5] According to the Health Canada summary safety review, the recommended population for immunization was females 9 to 45 years of age and males 9 to 26 years of age.[5] At the time, evidence from a series of large randomized controlled trials (RCTs) in 17,500 young women across four continents showed the vaccine was highly effective in preventing cervical, vaginal and vulvar neoplasias, and anogenital warts in women who had not already been exposed to the HPV types.[6]

In February 2015, Health Canada approved an expanded vaccine, Gardasil 9 (9V), that protects against an additional five HPV types (31, 33, 45, 52, 58).[7] The vaccines do not provide protection against diseases from vaccine HPV types to which a person has previously been exposed through sexual activity.[8] With the marketing of the 9V vaccine, the 9V vaccine has replaced availability of the 4V vaccine, at least in the US.[9]

The World Health Organization issued a position statement in 2014 on immunization for HPV recommending that HPV vaccines be included in national immunization

programs providing that: prevention of HPV-related diseases constitutes a public health priority; vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost-effectiveness of vaccination strategies in the country or region is considered. There was no specific mention of patient group.[2]

All jurisdictions in Canada have offered HPV immunization in publicly-funded programs for girls and young women since about 2007; however, vaccination was not initially offered to boys and young men.[10] However, as more evidence has been published about the benefits of immunizing young males, seven of 10 provinces have expanded their HPV vaccination programs to cover school-age boys including: Prince Edward Island (2013), Alberta (2014), British Columbia (high risk program for MSM, HIV and street-involved, 2015), Nova Scotia (2015), Manitoba (2016), Ontario (2016), and Quebec (2016).[10-13]

The purpose of the report is to review the evidence regarding HPV vaccination of males for the prevention of HPV infection and HPV-related genital warts and cancers in men.

Research Questions

1. What is the clinical effectiveness of HPV vaccination for males using the quadrivalent vaccine or 9-valent vaccine for preventing HPV infection and HPV-related genital warts and cancers of the penis, anus, or oropharynx in men?

2. What is the cost-effectiveness of HPV vaccination for males using the quadrivalent vaccine or 9-valent vaccine for preventing HPV infection and HPV-related genital warts and cancers of the penis, anus, or oropharynx in men?

3. What are the evidence-based guidelines regarding HPV vaccination in men?

Key Findings

A growing body of evidence supports the immunization of boys and young men (up to age 26), particularly with the approval of a 9V vaccine that expands the HPV types covered and additional types of cancers impacted. Recent national guidelines from Canada and the US now recommend including boys and young men in HPV immunization programs, as well as people who are immunocompromised and those with HIV. Additional evidence reviewed for this report has suggested there may be benefits to immunizing men over age 26, particularly high risk populations such as men who have sex with men, although more research is needed in this area. Economic analyses are generally favourable although are dependent on factors such as cost to purchase and administer the vaccine, and dosage schedules.

Methods

A limited literature search, with main concepts appearing in title or major subject heading, was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet

search. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between Jan 1, 2012 and Feb 24, 2017.

Literature Search Methods

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adolescent and adult males (ages ≥ 9 years); subgroup of interest ages 18 to 26
Intervention	Vaccination against HPV types 6, 11, 16, and 18 (Gardasil) or HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58 (Gardasil 9)
Comparator	No vaccination; alternative age of vaccination; vaccination in females
Outcomes	Q1: Clinical effectiveness (e.g., HPV infection rates, incidence of genital warts, pre-cancerous lesions, and cancers of the penis, anus, or oropharynx [back of the throat, including base of the tongue and tonsils]) as well as seroconversion Q2: Cost-effectiveness outcomes (e.g., cost per QALY or health benefit) Q3: Evidence-based guidelines for HPV vaccination in males, including recommended age or age range for vaccination
Study Designs	HTAs/systematic reviews/meta-analyses, RCTs, non-randomized studies, economic evaluations, clinical guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2011.

Critical Appraisal of Individual Studies

The included clinical studies were critically appraised using the Downs and Black tool[14] that assesses studies based on up to 27 criteria such as clear description of objectives, interventions, and outcomes; adequacy of statistical tests; and loss to follow-up. Economic studies were assessed using the Drummond checklist[15] and guidelines were assessed using the AGREE II instrument.[16] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 852 citations were identified in the literature search. Following screening of titles and abstracts, 800 citations were excluded and 52 potentially relevant reports from the electronic search were retrieved for full-text review. Two relevant publications were retrieved from the grey literature, hand searching, etc. (both were clinical guidelines). Of these potentially relevant articles, 36 publications were excluded for various reasons, while 18 publications met the selection criteria and were included in this report (seven clinical studies, eight economic analyses, and three clinical guidelines). Appendix 1 shows the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Clinical studies

No systematic reviews were identified. Included were seven primary studies reporting on HPV vaccination in boys or men:

(a) Three cohort studies (two prospective and one retrospective) focused on the 4V vaccine, one study in pre-teens and teens ages nine to 15,[17] and two in adults (Appendix 2, Table 2).[4,18]

(b) Four studies (one RCT and three prospective cohort) focused on the 9V vaccine, two studies in pre-teens and teens ages nine to 15,[19,20] and two in adults (Appendix 2, Table 3).[1,21]

With respect to the 4V vaccine (Appendix 2, Table 2), in an eight-year follow-up study in pre-teens and teens in the USA, Mexico, Norway, Denmark, Thailand (that followed an RCT),[6] 263 males who were at least 16 years old (mean age was not reported) were followed after vaccination at months 0, 2, and 6 starting in 2003, to determine their long-term anti-HPV 6/11/16/18 serum levels (an intermediate outcome). A secondary objective was vaccine effectiveness against HPV 6/11/16/18-related persistent infection or disease (a clinical outcome). Another prospective cohort study followed 150 men ages 27 to 45 in the USA and Mexico who received three doses of 4V vaccine over six months (months 0, 2 and 6) to assess durability of seroconversion.[4] Finally, a retrospective cohort study of 313 men-who-have-sex-with-men (MSM) age 26 or older (mean 42 years; range, 26 to 76) in the USA assessed the protection provided by the vaccine, given starting in 2006, with respect to development of anal warts over median follow-up of about three years.[18]

With respect to the 9V vaccine (Appendix 2, Table 3), two large, international, multicenter, prospective, immunogenicity cohort studies recruited boys and girls aged nine to 15 as well as young women aged 16 to 26.[19,20] The studies both aimed to measure immunogenicity after several versions of two-dose[19] or three-dose[20] vaccine regimens. The most recent 9V study in men 16–26 years of age(published in 2016) was an RCT conducted in 2014-15 in Belgium, Germany, and the Netherlands that assessed serological response to anti-HPV 6/11/16/18 for men who received the 9V vaccine versus the 4V vaccine, both given at months 0, 2, and 6.[21] The other study involving men was a large, international, multicenter, prospective, immunogenicity

cohort study that recruited men (including MSM) and women ages 16 to 26 to assess seroconversion a month after the last dose of a three-dose regimen of 9V vaccine.[1]

Adverse effects were reported in six of the included clinical studies, two for 4V[4,6] and four for 9V.[1,19-21]

Economic studies

Two systematic reviews of economic analyses[22,23] and six subsequent relevant economic studies[3,24-28] were located. The systematic reviews are briefly described here and the six primary studies more recent than the systematic reviews are described in the text and in Appendix 2, Table 4.

Systematic Reviews

The two systematic reviews overlapped in 11 studies with each review including several additional analyses.

Sinisgalli et al. (2015)[22] from Italy considered the economic implications of extending HPV vaccination from girls to boys. Their 15 included pharmaco-economic studies, published from 2005 to 2015, primarily included boys immunized in their 12th year (age range nine to 26 years). The V4 vaccine was assessed in all but two studies that used a bivalent vaccine for HPV types 14 and 16, and three-dose vaccines were used in all but one study (from Canada) that employed a two-dose vaccine.

Ben Hadj Yahia et al. (2015)[23] from France also considered extension of HPV vaccination from girls to boys based on clinical outcomes such as the occurrence of cervical cancer, anal cancer, and genital warts. Included were 17 economic analyses published from 2004 to 2014 that assessed three-dose vaccine series. The analyses were grouped by clinical outcomes with a separate analysis for MSM.

Primary Economic Analyses

Six economic analyses were published in 2015 and 2016, more recently than the two systematic reviews.[3,24-28] The analyses came from six countries: Canada, Chile, Italy, the Netherlands, the UK, and the USA. Four focussed on immunization of children or teens while two focussed on adult men. As approval of the 9V vaccine is recent, one analysis looked at the 9V vaccine with the others covering the 4V vaccine or a 2V vaccine (for HPV types 16 and 18) that is generally used only in females. One of the CEAs took a societal perspective while the others took some sort of health system perspective. Assumptions regarding the efficacy and uptake of vaccines varied between studies. Four analyses[3,24,26,28] reported results as cost per quality adjusted life-year (QALY) gained, while one[25] reported cost per disability adjusted life-year. One study[27] did not calculate specific cost-effectiveness ratios but modelled the number of vaccinations required to prevent one case of HPV-related cancer, which was used to determine a vaccine price at which vaccination of males was cost-effective. Details are contained in Appendix 2, Table 4 with results in Appendix 4, Table 11.

Clinical Practice Guidelines

Three relevant clinical guidelines from the US,[9] Canada,[10] and Ontario[29] were identified, with the two most recent and comprehensive guidelines being of particular interest: guidance from the US Advisory Committee on Immunization Practices (ACIP)

dated December 2016[9] and guidance from the National Advisory Committee on Immunization (NACI) for the Public Health Agency of Canada dated July 2016 (Appendix 2, Table 5).[10] The Ontario guideline highlighted the recommendations from the 2015 NACI guideline within the context of Ontario's HPV vaccination program in order to provide a position on two-dose schedules.[29]

Summary of Critical Appraisal

For the clinical studies (Appendix 3, Table 6), study design was a limitation: one study was an RCT but the other six were cohort studies, generally considered to be a lower quality study design. Two smaller studies (n= 313[18] and n=263[6]) tracked patients through to occurrence of disease, with the others employing seroconversion, an indirect outcome. Generally the follow-up was short, extending to one month after the last injection in five studies.[1,4,19-21] While this follow-up duration is may be appropriate for seroconversion outcomes, it may be insufficient for longer term adverse events. The studies reporting clinical outcomes had longer follow-up of 8 years[6] and 981 days[18] though it is unclear whether this is sufficient to detect development of HPV-related cancers. Study enrollees were generally not well described and it was often unclear how representative the populations and the study settings were of the population as a whole. Recruitment criteria were not well described, as was information about people lost to follow-up. All included studies were clear about their objectives, interventions, outcomes tracked, and findings (including adverse effects).

As it concerns the two systematic reviews of economic studies,[22,23] the methods described in the reports of findings were generally of poor quality. While both SRs did include a list of included studies and their features, neither included any description of an *a priori* design; duplicate source selection; nor duplicate data abstraction. Literature search methods were deemed adequate in one SR,[23] but the other sought sources from PubMed alone.[22] One SR reported an assessment of the quality of included studies in its methods[23] however, the results of this assessment were not reported. Finally, publication bias was not addressed in either SR; nor was the impact of study quality or sources of funding for included studies.

For the primary economic studies (Appendix 3,Table 7), rationale, objectives, design and viewpoint were all clearly described, with the exception of one study that did not explicitly describe the viewpoint informing the study's design.[26] Data sources used to inform effectiveness estimates were identified in all primary economic studies, but details describing these sources were rarely included. Details concerning models used, adapted or developed were generally reported clearly by all of the included studies.

Generally, the primary outcome(s) of interest for each study were clearly identified; however indirect benefits were not addressed in depth by any of the included studies. Consideration of price adjustments and/or inflation were not always reported, nor reported in adequate detail so as to allow the reader to assess the appropriateness of the method used.[25,26,28] Study time horizons and discount rates were consistently reported, but an explicit justifications for discount rate selection was missing from one study.[24] Methods for handling stochastic data were generally not reported in detail by any of the included studies. And while sensitivity analyses were generally reported clearly and in sufficient detail, a justification for the selection of included variables was

not always reported clearly.[3,25,26,28] For all included primary economic studies, appropriate conclusions were presented.

For the clinical guidelines (Appendix 3, Table 8), development methodology was described in brief or not at all, including the links between the evidence and the recommendations. Both the US guideline[9] and the NACI guideline[10] stated they were based on a systematic review of the evidence, though details of the review were not provided. The Ontario guideline[29] was based on the recommendations by NACI and adapted for the Ontario context. All guidelines involved extensive expert panels. None of the three described patient involvement or perspectives, and none included specific details about the vaccines' health benefits, adverse effects, and other risks. Cost was not discussed and issues related to implementation were only mentioned in the guideline from Public Health Ontario.[29] None of the guidelines mentioned external review, validation, or plans for updating.

Summary of Findings

What is the clinical effectiveness of HPV vaccination for males using the quadrivalent vaccine or 9-valent vaccine for preventing HPV infection and HPV-related genital warts and cancers of the penis, anus, or oropharynx in men?

With respect to the 4V vaccine and clinically meaningful outcomes, results from the long-term prospective cohort study in pre-teens and teens,[17] showed no HPV-related disease plus durability of protection serologically at eight years of follow-up (85% to 99% depending on HPV type, Appendix 4, Table 9). The retrospective cohort study of 313 MSM age 26 or older found that the vaccine provided some protection because the rate of anal warts was 3.7 versus 7.3 per 100 person-years for vaccinated versus unvaccinated men, respectively (p=0.05).[18] With respect to serological conversion alone, a second prospective cohort study of 150 men ages 27 to 45 reported that at month 7 (a month after the last dose), 100% of the men had seroconverted to each of the four HPV vaccine components.[4]

No studies of the 9V vaccine included clinical outcomes (Appendix 4, Table 10). The results of the two large, prospective, immunogenicity three-cohort studies in boys and girls aged nine to 15 as well as young women aged 16 to 26 showed complete seroconversion in boys, with results that were non-inferior to those found for the young women.[19,20] The RCT assessing serological response to anti-HPV 6/11/16/18 for men who received the 9V versus the 4V vaccine showed that anti-HPV seroconversion to the HPV types covered by the 4V vaccine was no different between the two vaccines.[21] The fourth study that recruited men (including MSM) and women ages 16 to 26 to assess seroconversion a month after the last of a three-dose regimen of 9V vaccine found that over 99.5% of the enrollees were seropositive a month after the third injection.[1]

Adverse effects were reported in six of the included clinical studies, two for 4V[4,6] and four for 9V.[1,19-21]

Ferris et al. (2014),[6] in their single-arm 8-year extension of an RCT (n=263 males age 16+ years in the study extension) reported no new significant serious adverse events observed after 4V vaccination in both genders. (The adverse effects in the original RCT were not discussed).

Giuliano et al. (2015),[4] a prospective cohort study assessing the immunogenicity and safety of 4V vaccine in 150 men age 27 to 45, had subjects complete a vaccine report card to document any adverse effects for 14 days following each of three doses of vaccine. Sixty-three men (42%) reported a total of 107 vaccine-related events, 47% of which were injection-site-related, and 53% of which were systemic. The most common systemic adverse event reported was headache, followed by nasal congestion, with all adverse events graded as mild to moderate. No serious adverse effects were reported.

Iverson et al. (2016),[19] in their international prospective cohort non- inferiority immunogenicity study of 9V vaccine covering ages 9 to 26 (1,518 enrolled of which 451 were boys aged 9 to 15), reported that 22 participants experienced serious adverse events none of which were considered related to the vaccine. The publication did not separate adverse effects by sex, nor did it report less serious adverse effects.

Similarly, van Damme et al. (2015),[20] in their international prospective cohort non-inferiority immunogenicity study of 9V vaccine covering ages 9 to 26 (3,066 enrolled of which 669 were boys aged 9 to 15), had participants complete a vaccine record for 15 days after each vaccination to capture injection-site and systemic adverse effects. The most common injection site effects (incidence ≥ 2%) were pain, swelling, erythema, and pruritus; most were mild to moderate in intensity. The most common (incidence ≥ 2%) vaccine-related systemic adverse effects were headache and pyrexia. A 10-year-old boy with a history of allergies and asthma experienced a serious adverse event attributed to the vaccine: an asthma exacerbation one day after receiving dose 1 that required hospitalization for one day.

van Damme et al. (2016) also conducted an RCT[21] of the safety and immunogenicity of 9V versus 4V vaccines in 500 men aged 16 to 26 years. Occurrence of adverse effects was similar between study arms with about 75% reporting local injection site reactions (erythema, swelling, pain) and no serious adverse events in either group

Finally, Castellsagué et al. (2015),[1] in their prospective cohort immunogenicity study of 9V in both sexes aged 16 to 26 (including 1100 heterosexual men and 300 MSM), reported local injection site reactions (erythema, swelling, pain, or pruritus) in 68% of male participants with no serious adverse effects, and systemic vaccine-related effects in 16% of participants (headache, fever, or nausea) but no serious vaccine-related events.

What is the cost-effectiveness of HPV vaccination for males using the quadrivalent vaccine or 9-valent vaccine for preventing HPV infection and HPV-related genital warts and cancers of the penis, anus, or oropharynx in men?

With respect to the two overlapping systematic reviews:

The Italian systematic review concluded that a universal gender-neutral HPV vaccination program including boys (age not specified) could greatly reduce the incidence of new HPV infections and is likely to be cost-effective and economically sustainable, considering current vaccine prices and the two-dose schedule.[22] They noted that previously published economic evaluations had shown controversial and unfavourable cost-effectiveness of universal vaccination; however, they reanalyzed

their included reviews in light of decreased vaccine costs and a 2-dose versus 3-dose schedule and found all analyses to be favourable or possibly favourable.

The systematic review from France concluded that extending vaccination to males is not cost-effective when only select HPV-related diseases were considered (cervical cancer, cervical cancer combined with genital warts, and anal cancer and/or genital warts when only MSM populations are considered). However, when all HPV-related diseases are considered (cervical, vaginal, vulvar, penile, anal, and oropharyngeal cancers, juvenile or/and adulthood-onset recurrent respiratory papillomatosis and genital warts), vaccine coverage is below 40%, and/or vaccine price is less than USD $75, cost-effectiveness is more favourable. They determined that vaccination of the MSM group is cost-effective.[23]

With respect to the primary studies (Appendix 4, Table 11), of particular interest was a CEA from Toronto, Canada, that assessed the cost-effectiveness of vaccinating boys age 12 with the 4V vaccine versus vaccination of girls only and the impact on occurrence of oropharyngeal cancer.[28] The analysis was performed from a Ministry of Health perspective. Results showed vaccination of boys to be cost-saving whether the vaccine efficacy and uptake were low (50% and 50%) or high (98% and 79%). For a theoretical cohort of 12-year-old boys across Canada (about 200,000 a year), according to the study this intervention could save $8 million to $28 million over the lifetime of this cohort of boys due to reductions in oropharyngeal cancer alone.

A study of 9V from the US[3] calculated that switching to 9V vaccination from 4V in adolescents and young adults would lead to substantial reductions in cervical lesions and cancers, and cost savings in managing cervical lesions would be greater than the additional costs of the 9V program as long as the additional 9V cost/dose (versus 4V) is less than $13. The conclusion was that giving females 9V would provide the majority of benefits of a gender neutral strategy.

A Dutch study[27] calculated a 37% (28% to 48%) reduction in vaccine-preventable HPV cancers if vaccine uptake by girls is at the current level of 60%. Males benefit indirectly from vaccination of girls but some remain at risk of cancers associated with HPV. The incremental benefit of vaccinating boys when vaccine uptake among girls is high occurs because of the prevention of anal carcinomas in men, and this particularly justifies HPV prevention efforts for MSM.

In an Italian study[26] examining immunizing boys and girls around age 12, universal HPV vaccination was found to be cost-effective versus either cervical cancer screening or female-only vaccination. In comparison with cervical cancer screening alone, universal vaccination led to an incremental cost-effectiveness ratio (ICER) of €1,500 and when compared with female-only vaccination, universal vaccination was considered cost-effective with an ICER of €11,600.

Two studies in men assessed subpopulations: HIV positive men[25] and MSM who were HIV positive or negative.[24]

A Chilean study of the effect of 4V vaccination in men aged 25 to 34 on the occurrence of anal cancer did not find the intervention to be cost-effective with a calculated disability adjusted life year (DALY) estimate of about USD $140,000.[25] The

study assumed the vaccine cost to be USD $132 and vaccine efficacy to be in the range of 65%.

In contrast, a UK CEA that considered offering 4V vaccine to men aged 16 to 40 at genitourinary clinics concluded that vaccination could be cost-effective for MSM who regularly access specialist sexual health services if vaccine purchase and administration costs were under about USD $120 per patient. (They performed analyses using vaccine costs equivalent to about USD $120 but also $60.) Vaccine efficacy was modelled from a low of about 52% to a high of 82%. These authors noted that the largest reductions in HPV-related disease will occur through universal vaccination of pre-adolescent boys because many MSM initiate same-sex activity early. They also concluded that gender-neutral vaccination of 12-year-olds does not preclude offering vaccination to MSM up to a higher age, particularly because some MSM are born in countries that do not currently immunize boys.[24]

What are the evidence-based guidelines regarding HPV vaccination in men?

Both the US Advisory Committee on Immunization Practices[9] and the (Canadian) National Advisory Committee on Immunization[10] recommend routine immunization of boys and girls around age 12 but also of young men (to age 21 for the US guidelines with immunization up to age 26 for MSM and transgender persons who were not adequately vaccinated previously, and to age 26 for the Canadian guidelines) (Appendix 4, Table 12). Both guidelines also recommend immunizing (with the 3-dose regimen) immunocompromised individuals and immunocompetent HIV-infected individuals (age up to 26 for the US guidelines; age was not specified in the Canadian guidelines).[9,10] The Ontario guideline from April 2015 did not include routinely immunizing males, although did advise HPV vaccine for individuals who are immunocompromised, and immunocompetent HIV-infected individuals.[29]

Limitations

Most of the clinical evidence does not follow patients through to clinically meaningful outcomes, rather assessing seroconversion as an intermediate outcome. Also, the focus in the literature, particularly for the economic analyses, was on the 4V vaccine that is increasingly being replaced by the newly approved expanded 9V vaccine. This makes it difficult to determine what the HPV vaccination impact would be of immunizing Canadian males with current vaccines (and at what age) on reductions in HPV-associated disease long term.

Conclusions and Implications for Decision or Policy Making

Although HPV vaccination using the 4V vaccine started in Canadian school-based immunization programs in girls and young women about 10 years ago, immunization of boys and young men was not included at that time. A growing body of evidence supports the inclusion of boys and young men (to age 26) in HPV immunization programs, particularly with the approval of a 9V vaccine that expands the HPV types covered and additional types of cancers impacted.[7] July 2016 national Canadian guidelines[10] and December 2016 national US guidelines[9] recommend including boys and young men in HPV immunization programs. The Canadian guidelines specify extension to males up to age 26,{59} and the US guidelines specify age 21 but say this can be extended to age 26.[9] All guidelines recommend immunizing people with

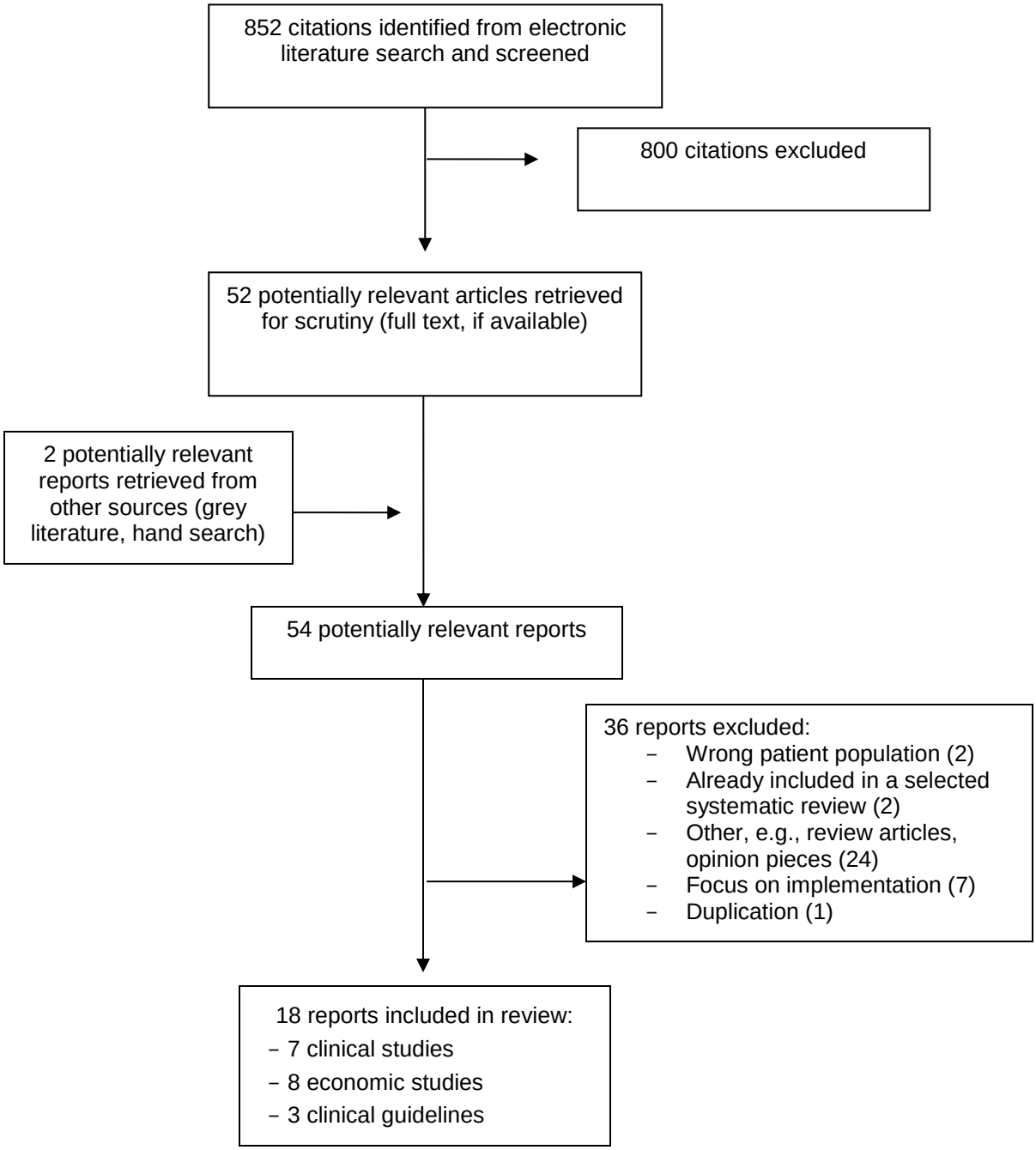
HIV and those who are immunocompromised.[9,10,29] Additional evidence reviewed for this report suggested there may be benefits to immunizing men over age 26,[4,18] particularly high risk populations such as MSM,[18] although more research is needed in this area. Economic analyses are generally favourable although are dependent on factors such as cost to purchase and administer the vaccine, and dosage schedules.

References

1. Castellsagué X, Giuliano AR, Goldstone S, Guevara A, Mogensen O, Palefsky JM, et al. Immunogenicity and safety of the 9-valent HPV vaccine in men. Vaccine. 2015 Nov 27;33(48):6892-901.
2. Human papillomavirus vaccines: WHO position paper, October 2014. Wkly Epidemiol Rec [Internet]. 2014 Oct 24 [cited 2017 Feb 27];89(43):465-91. Available from: http://www.who.int/wer/2014/wer8943.pdf
3. Brisson M, Laprise JF, Chesson HW, Drolet M, Malagon T, Boily MC, et al. Health and economic impact of switching from a 4-valent to a 9-valent HPV vaccination program in the United States. J Natl Cancer Inst. 2016 Jan;108(1).
4. Giuliano AR, Isaacs-Soriano K, Torres BN, Abrahamsen M, Ingles DJ, Sirak BA, et al. Immunogenicity and safety of Gardasil among mid-adult aged men (27-45 years)--The MAM Study. Vaccine. 2015 Oct 13;33(42):5640-6.
5. Summary safety review - Gardasil (quadrivalent human papillomavirus [types 6, 11, 16, 18] recombinant vaccine) - assessing general safety with a focus on autoimmune and cardiovascular diseases [Internet]. Ottawa: Health Canada; 2015 Dec 9. [cited 2017 Mar 8]. Available from: http://www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/gardasil-eng.php
6. Ferris D, Samakoses R, Block SL, Lazcano-Ponce E, Restrepo JA, Reisinger KS, et al. Long-term study of a quadrivalent human papillomavirus vaccine. Pediatrics [Internet]. 2014 Sep [cited 2017 Feb 27];134(3):e657-e665. Available from: http://pediatrics.aappublications.org/content/pediatrics/134/3/e657.full.pdf
7. Gardasil 9: summary basis of decision [Internet]. Ottawa: Health Canada; 2016. [cited 2017 Mar 8]. Available from: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2015_gardasil9_170006-eng.php
8. MerckVaccines.com [Internet]. West Point (PA): Merck & Co., Inc. Gardasil 9; 2016 [cited 2017 Mar 9]. Available from: https://www.merckvaccines.com/Products/Gardasil9
9. Meites E, Kempe A, Markowitz LE. Use of a 2-dose schedule for human papillomavirus vaccination - updated recommendations of the advisory committee on immunization practices. MMWR Morb Mortal Wkly Rep [Internet]. 2016 Dec 16 [cited 2017 Feb 27];65(49):1405-8. Available from: https://www.cdc.gov/mmwr/volumes/65/wr/pdfs/mm6549a5.pdf
10. National Advisory Committee on Immunization (NACI). An advisory comittee statement: updated recommendations on human papillomavirus (HPV) vaccines: 9-valent HPV vaccine and clarification of minimum intervals between doses in the HPV immunization schedule [Internet]. Ottawa: Public Health Agency of Canada; 2016. [cited 2017 Mar 9]. Available from: http://www.healthycanadians.gc.ca/publications/healthy-living-vie-saine/human-papillomavirus-9-valent-vaccine-update-recommendation-mises-a-jour-recommandations-papillome-humain-vaccin-nonavalent/alt/hpv-phv-eng.pdf
11. Human papillomavirus (HPV) vaccination program [Internet]. Québec: Government of Québec; 2017. [cited 2017 Mar 15]. Available from: http://sante.gouv.qc.ca/en/programmes-et-mesures-daide/programme-de-vaccination-contre-les-infections-par-les-virus-du-papillome-humain-vph/
12. Manitoba's HPV Immunization Program: questions & answers for health care providers [Internet]. Winnipeg (MB): Government of Manitoba; 2017. [cited 2017 Mar 15]. Available from: http://www.gov.mb.ca/health/publichealth/cdc/docs/hpv_phn_qa.pdf
13. Ontario extending free HPV vaccines to boys [Internet].CTV News; 2017. [cited 2017 Mar 15]. Available from: http://www.ctvnews.ca/health/ontario-extending-free-hpv-vaccines-to-boys-1.2869481
14. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2017 Mar 8];52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf
15. Higgins JPT, editors. Cochrane handbook for systematic reviews of interventions [Internet]. Version 5.0.2. Drummond. Oxford (United Kingdom): The Cochrane Collaboration; 2009. Figure 15.5.a: Drummond checklist. [cited 2017 Mar 15]. Available from: http://handbook.cochrane.org/chapter_15/figure_15_5_a_drummond_checklist_drummond_1996.htm
16. Brouwers M, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in healthcare. CMAJ [Internet]. 2010 Dec [cited 2017 Feb 27];182(18):E839-E842. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3001530/pdf/182e839.pdf
17. McCormack PL. Quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine (Gardasil®): a review of its use in the prevention of premalignant anogenital lesions, cervical and anal cancers, and genital warts. Drugs. 2014 Jul;74(11):1253-83.
18. Swedish KA, Goldstone SE. Prevention of anal condyloma with quadrivalent human papillomavirus vaccination of older men who have sex with men. PLoS ONE [Internet]. 2014 [cited 2017 Feb 27];9(4):e93393. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3979673
19. Iversen OE, Miranda MJ, Ulied A, Soerdal T, Lazarus E, Chokephaibulkit K, et al. Immunogenicity of the 9-valent HPV vaccine using 2-dose regimens in girls and boys vs a 3-dose regimen in women. JAMA [Internet]. 2016 Dec 13 [cited 2017 Feb 27];316(22):2411-21. Available from: http://jamanetwork.com/journals/jama/fullarticle/2588254
20. Van Damme P, Olsson SE, Block S, Castellsague X, Gray GE, Herrera T, et al. Immunogenicity and safety of a 9-valent HPV vaccine. Pediatrics [Internet]. 2015 Jul [cited 2017 Feb 27];136(1):e28-e39. Available from: http://pediatrics.aappublications.org/content/pediatrics/136/1/e28.full.pdf
21. Van Damme P, Meijer CJ, Kieninger D, Schuyleman A, Thomas S, Luxembourg A, et al. A phase III clinical study to compare the immunogenicity and safety of the 9-valent and quadrivalent HPV vaccines in men. Vaccine. 2016 Jul 29;34(35):4205-12.
22. Sinisgalli E, Bellini I, Indiani L, Sala A, Bechini A, Bonanni P, et al. HPV vaccination for boys? A systematic review of economic studies. Epidemiol Prev [Internet]. 2015 Jul [cited 2017 Feb 27];39(4 Suppl 1):51-8. Available from: http://www.epiprev.it/materiali/suppl/2015/EP2015_V4S1_051.pdf
23. Yahia MBBH, Jouin-Bortolotti A, Dervaux B. Extending the human papillomavirus vaccination programme to include males in high-income countries: a systematic review of the cost-effectiveness studies. Clin Drug Investig. 2015 Aug;35(8):471-85.
24. Lin A, Ong KJ, Hobbelen P, King E, Mesher D, Edmunds WJ, et al. Impact and cost-effectiveness of selective human papillomavirus vaccination of men who have sex with men. Clin Infect Dis. 2016 Dec 23. Epub ahead of print.
25. Parada CV, Veerman JL. Cost-effectiveness study of HPV vaccination as a primary prevention strategy for anal cancer in HIV-positive men in Chile. Value Health Reg Issues. 2016 Dec;11:17-23.
26. Haeussler K, Marcellusi A, Mennini FS, Favato G, Picardo M, Garganese G, et al. Cost-effectiveness analysis of universal human papillomavirus vaccination using a dynamic Bayesian methodology: the BEST II study. Value Health [Internet]. 2015 Dec [cited 2017 Feb 27];18(8):956-68. Available from: http://www.sciencedirect.com/science/article/pii/S1098301515020471

27. Bogaards JA, Wallinga J, Brakenhoff RH, Meijer CJ, Berkhof J. Direct benefit of vaccinating boys along with girls against oncogenic human papillomavirus: Bayesian evidence synthesis. BMJ [Internet]. 2015 May 12 [cited 2017 Feb 27];350:h2016. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4428278
28. Graham DM, Isaranuwatchai W, Habbous S, de Oliveira C, Liu G, Siu LL, et al. A cost-effectiveness analysis of human papillomavirus vaccination of boys for the prevention of oropharyngeal cancer. Cancer [Internet]. 2015 Jun 1 [cited 2017 Feb 27];121(11):1785-92. Available from: http://onlinelibrary.wiley.com/doi/10.1002/cncr.29111/full
29. Provincial Infectious Diseases Advisory Committee. Recommendations for human papillomavirus (HPV) vaccine schedule [Internet]. Toronto: Public Health Ontario; 2015. [cited 2017 Mar 10]. Available from: https://www.publichealthontario.ca/en/eRepository/HPV_Vaccine_Schedule_Recommendations.pdf
30. Saraiya M, Unger ER, Thompson TD, Lynch CF, Hernandez BY, Lyu CW, et al. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. J Natl Cancer Inst [Internet]. 2015 Jun [cited 2017 Feb 27];107(6):djv086. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4838063

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Clinical Studies of 4 Valent Vaccine

First Author (Year); Country	Study Type	Population Characteristics	Intervention (and Comparator If applicable)	Clinical Outcomes, Follow-up
In Pre-Teens and Teens				
Ferris et al. (2014);[6] USA, Mexico, Norway, Denmark, Thailand	Long-term cohort study of safety, immunogenicity, and effectiveness (following a 1-year RCT)	*Initial RCT*: sexually naive boys and girls, 9 to 15 years (n=1781) x 1 year; follow-up at 8 years, age ≥16 years. *Follow-up cohort study*: 263 males, required to be age ≥16 years but their characteristics NR.	*RCT intervention*: HPV vaccine, day 1 and months 2 and 6 assigned 2:1 with controls who received saline injections according to the same initial schedule At 30 months, the control group received the same 3-dose HPV vaccine regimen ("catch-up vaccination group")	Primary objective was to evaluate the long-term anti-HPV 6/11/16/18 serological levels; secondary objective was to estimate vaccine effectiveness against HPV 6/11/16/18-related persistent infection or disease. Follow-up at 96 months (8 years).
In Adults				
Giuliano et al. (2015),[4] USA and Mexico	Prospective cohort study assessing the immunogenicity and safety.	Men age 27 to 45 years (median 36 years) (n=150); 45% white race and 43% Native American; 12% ever MSM; 62% married or cohabiting. At enrollment, a small percentage had detectable levels of anti-HPV antibodies in serum: HPV 6 (18.0%), 11(6.0%), 16 (13.3%), or 18 (7.3%)	Gardasil administered at Day 1 and Months 2 and 6. Sera were collected pre-vaccination and Month7 (one month post-dose three) to test anti-HPV6, 11, 16, and 18 IgG levels.	Anti-HPV 6/11/16/18 IgG levels. Follow-up at 7 months.
Swedish et al. (2014),[18] USA	Post-hoc (retrospective) analysis of a cohort study	MSM age ≥ 26 years (mean 42 years, range 26 to 76) (n=313), HIV-negative, no prior history of anal condyloma (n=210) or previously-treated recurrence free for 12+ months (n=103); 116 previously vaccinated versus 197 never vaccinated. Vaccinated group significantly younger (38.6 vs 44.3 years), and more likely to smoke (21.6% vs 13.2%).	Retrospectively compared those who had received 3-dose vaccine versus those with no vaccine. (Those with incomplete vaccination not included.)	Development of anal condyloma as related to vaccine status. Follow-up median 981 days.

MSM = men who have sex with men; NA = not applicable; NR = not reported; RCT = randomized controlled trial

Table 3: Characteristics of Clinical Studies of 9 Valent Vaccine

First Author (Year); Country	Study Type	Population Characteristics	Intervention	Clinical Outcomes, Follow-up
In Pre-Teens and Teens				
Iverson et al. (2016);[19] 52 sites in 15 countries (lead is from Norway).	Prospective cohort non-inferiority immunogenicity study (5 cohorts: 4 of girls and boys aged 9 to 15 with varying vaccine schedules and one of young women aged 16 to 26).	Enrolled = 1518; 451 were boys aged 9 to 15 years (mean age 11.5); boys were divided into two groups – one received 9V vaccine at 0 and 6 months (n=306), the other received 9V vaccine at 0 and 12 months (n=150).	2-dose 9V vaccine administered 6 or 12 months apart or 3-dose 9V administered over 6 months.	Antibody response against each HPV type assessed 1 month after last dose. Systemic and injection-site AEs and serious AEs. Follow-up 4 weeks after last dose (but ultimately planned for 36 months).
Van Damme et al. (2015);[20] 72 sites in 17 countries (lead is from Belgium).	Prospective cohort non-inferiority immunogenicity study (3 cohorts: girls and boys aged 9 to 15 and young women aged 16 to 26).	Enrolled = 3066; 669 were boys aged 9 to 15 years (median age 12); race 44% white, 28% Asian, 23% mixed.	3-dose 9V vaccine regimen administered at Day 1, Month 2, and Month 6.	Anti-HPV serologic assays were performed at Day 1 and Month 7. Systemic and injection-site AEs and serious AEs. Follow-up 2.5 years (36 months).
In Adults				
van Damme et al. (2016);[21] 7 sites in 3 countries (Belgium, Germany, and the Netherlands)	RCT of the safety and immunogenicity of 9V versus 4V vaccines in men aged 16 to 26 years.	Enrolled = 500 men aged 16 to 26 years (mean 21) in good physical health, history of ≤ 5 lifetime female and no male sexual partners.	Blinded randomization via an IWRS to 3-dose 4V or 9V vaccine on Day 1, Month 2, and Month 6.	Anti-HPV antibody responses at Month 7 for each of 6/11/16/18 (to compare 4V and 9V) and 31/33/45/52/58.
Castellsagué et al. (2015);[1] 76 sites in 17 countries (lead is from Spain).	Prospective cohort immunogenicity study (3 cohorts: men, women and MSM), age group 16 to 26	Enrolled = 1100 heterosexual men, 1100 women, 300 MSM; mean age 21 years	3-dose 9V vaccine regimen administered at Day 1, Month 2, and Month 6.	Anti-HPV antibody responses at Month 7 for HPV 6/11/16/18/31/33/45/52/58.

AE = adverse event; HPV = human papilloma virus; IWRS = Interactive Web Response System; MSM = men who have sex with men; RCT = randomized controlled trial

Table 4: Characteristics of Economics Studies

First Author (Year); Country	Type of Analysis, Time Horizon, Study Perspective	Patient Population	Intervention & Comparator	Assumptions
Systematic Reviews				
Sinisgalli (2015);[3] Italy	Systematic review of economic evaluations describing 15 individual economic studies published between 2005 and 2015	Extension of HPV vaccination to boys (age not specified)	Extension of HPV vaccination to boys (age and vaccine not specified) compared with female-only vaccination	NA
Yahia (2015);[23] France	Systematic Review of economic evaluations describing 17 studies published between 2001 and 2014	Vaccination of males (age not specified)	Vaccination of males and females versus females only or screening only	NA
Primary Economic Analyses				
Brisson (2016);[3] USA	CEA and population-level effectiveness of switching from 4V to 9V vaccine in the USA; 70-year time horizon; societal perspective	Unclear. Assumed females age 11 to 26 years and males age 11 to 21 years as per cited guidelines	9V vaccine versus 4V vaccine	95% vaccine efficacy Lifelong protection Cost/dose of $145 (4V) and $158 (9V)
Lin (2016);[24] UK	CEA and potential health impact of offering 4V vaccination at genitourinary clinics in England; 100-year time horizon; health care provider perspective	MSM with and without HIV ages 16 to 40 in four age bands	4V vaccine versus no vaccine	Vaccine protection wanes at 20 years Vaccines protect against laryngeal cancer 100% 3-dose completion rate No herd protection, so vaccines only reduce the risk of infection in those vaccinated
Parada (2016);[25] Chile	CEA; lifetime time horizon; public health system perspective	HIV positive men in Chile aged 25 to 34	4V vaccine versus no vaccine	Vaccine cost USD $132 Vaccine wastage15% Vaccine admin costs per dose USD $10 Vaccine coverage 70% Vaccine efficacy 50.3% ITT, 77.5% PP 0% remission rate of anal cancer Survival rate with anal cancer at least 5 years
Bogaards (2015);[27] Netherlands	Economic model (bayesian evidence synthesis approach)	Boys age 12	2V vaccine (HPV types 16 and 18)	Two different vaccine uptake rates in girls (60% and 90%) and projected the same for boys HPV-related tumours in MSM determined by MSM population prevalence and their relative risks of HPV-associated cancers Benefit only accrues to boys vaccinated

Table 4: Characteristics of Economics Studies

First Author (Year); Country	Type of Analysis, Time Horizon, Study Perspective	Patient Population	Intervention & Comparator	Assumptions
Graham (2015);[28] Canada	CEA; lifetime time horizon; Ministry of Health perspective	Boys age 12	4V vaccine versus no vaccine	Vaccine efficacy 83.8% Vaccine uptake 50%
Haeussler, (2015);[26] Italy	CEA of universal vaccination; 55 year time horizon; health system perspective (direct medical costs associated with screening, diagnosis, and management of HPV-related diseases)	Boys age 12	Universal 4V versus female-only 4V versus cervical screening only	Vaccine efficacy for cancer of the cervix, anus, head and neck = 78%, 70%, 50%, respectively Vaccine uptake 90%

CEA = cost-effectiveness analysis; ITT = intention to treat; MSM = men who have sex with men; NA = not applicable; PP = per protocol

Table 5: Characteristics of Included Clinical Guidelines

Objectives			Methodology			
Intended Users/Target Population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence Collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations Development and Evaluation**	**Guideline Validation**
US Advisory Committee on Immunization Practices (ACIP), December 2016[9] (Meites et al 2016)						
Health care providers/ children and young adults	HPV vaccination (2V, 4V and 9V), 2-dose and 3-dose	Immunogenicity (seroconversion) plus important or critical health outcomes	SR performed, focus on studies of boys and girls 9-14 with 2-dose 9V vaccine (literature search end date NR)	Assessed using GRADE	Developed using the GRADE framework, posted for public comment, and passed by an ACIP member vote	NR
National Advisory Committee on Immunization (NACI) (Public Health Agency of Canada), July 2016[10]						
Health care providers/ children and young adults	HPV vaccination (2V, 4V and 9V – focus on 9V), 2-dose and 3-dose	Burden of illness to be prevented; vaccine effectiveness, safety, and schedules	Systematic search of clinical (economic literature was excluded) to May 2015	NR	NACI and the HPV WG considered the evidence, including unpublished material, and developed recommendations	NR
Public Health Ontario: Provincial Infectious Diseases Advisory Committee (2015)[29]						
Health care providers/ children and young adults	HPV vaccination (2V and 4V), 2-dose and 3-dose – focus on 2-dose	NR	NR – this Ontario document is described as being a locally adapted version of the NACI (2012) recommendations		NR	NR

ACIP = Advisory Committee on Immunization Practices; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HHPV = human papilloma virus; NACI = National Advisory Committee on Immunization; NR = not reported; WG = working group

Appendix 3: Critical Appraisal of Included Publications

Table 6: Critical Appraisal of Included Clinical Studies

First Author, Year	Strengths	Limitations
4V Vaccine in Pre-Teens and Teens		
Ferris et al. (2014)[6]	Clear objectives, outcomes, interventions, main findings, adverse effects Followed enrollees through to disease occurrence at 8 years	Weak study design (cohort) Population characteristics for males in the long-term cohort study of interest not described (aside from age ≥ 26 years) Patients lost to follow-up not described Not clear how subjects were recruited
4V Vaccine in Adults		
Giuliano et al. (2015)[4]	Clear objectives, outcomes, interventions, main findings, adverse effects Characteristics of patients described AEs reported in detail No loss to follow-up	Weak study design (cohort) Unclear how representative the included patients and the setting were Follow-up only 7 months so vaccine duration unknown Indirect outcome (immunogenicity)
Swedish et al. (2014)[18]	Clear objectives, outcomes, interventions, main findings, AEs Characteristics of patients in both groups described and compared Length of follow-up taken into account Clinical outcome (anal condylomata)	Weak study design (cohort) Unclear how representative the included patients and the setting were Vaccinated and unvaccinated populations differed in several ways, including length of follow-up
9V Vaccine in Pre-Teens and Teens		
Van Damme et al. (2015)[20]	Clear objectives, outcomes, interventions, compliance rates, main findings, AEs Characteristics of patients in all groups described and compared	Weak study design (cohort) Losses to follow-up itemized but characteristics not described Unclear how representative the included patients and the setting were Indirect outcome (immunogenicity)
Iverson et al. (2016)[19]	Clear objectives, outcomes, interventions, compliance rates, main findings, AEs Characteristics of patients in all groups described and compared	Weak study design (cohort) Losses to follow-up itemized but characteristics not described Unclear how representative the included patients and the setting were Indirect outcome (immunogenicity)
9V Vaccine in Adults		
Van Damme et al. (2016)[21]	Strong study design (RCT) Clear objectives, outcomes, interventions, main findings AEs reported in detail	Losses to follow-up itemized but characteristics not described (though rate was very low) Unclear how representative the included patients and the setting were Description of enrollees is limited Indirect outcome (immunogenicity)
Castellsagué et al. (2015);[1]	Clear objectives, outcomes, interventions, main findings Recruitment settings described AEs reported in detail	Weak study design (cohort) Losses to follow-up itemized but characteristics not described Indirect outcome (immunogenicity)

AE = adverse effect; RCT = randomized controlled trial

Table 7: Critical Appraisal of Included Economic Studies

First Author, Year, Country	Strengths	Limitations
Systematic reviews		
Sinisgalli (2015);[22]	• Included studies described	• *A priori* study design not reported • Literature search used only 1 database • Duplicate study selection/abstraction not reported • Publication status not considered • No study quality assessment was described • Publication bias not addressed • Funding sources not reported
Yahia (2015);[23]	• Literature search was adequate • Sources included regardless of publication status • Included studies described • Quality assessment of included studies reported	• *A priori* study design not reported • Duplicate study selection/abstraction not reported • Impact of study quality on reported findings not addressed • Publication bias not addressed • Funding sources not reported
Economic evaluations		
Brisson (2016);[3] USA	• Study objectives, rationale, viewpoint and design reported clearly • Data sources described and referenced • Model(s) described in detail	• Indirect benefits not addressed explicitly • Methods for handling stochastic data not detailed • Justification for selection of variables in sensitivity analyses not detailed
Lin (2016);[24] UK	• Study objectives, rationale, viewpoint and design reported clearly • Data sources described and referenced • Model(s) described in detail • Sensitivity analyses described and justified	• Methods for valuation of benefits not explicitly described • Indirect benefits not addressed explicitly • Choice of discount rate not justified • Methods for handling stochastic data not detailed
Parada (2016);[25] Chili	• Study objectives, rationale, viewpoint and design reported clearly • Data sources described and referenced • Model(s) described in detail	• Methods for valuation of benefits not explicitly described • Indirect benefits not addressed explicitly • Consideration of inflation not reported • Methods for handling stochastic data not detailed • Justification for selection of variables in sensitivity analyses not detailed
Bogaards (2015);[27] Netherlands	• Study objectives, rationale and design reported clearly • Data sources for clinical parameters described and referenced • Model described in detail • Sensitivity analyses described	• Not a true cost-effectiveness evaluation. Study reported QALYs and number needed to vaccinated and calculated vaccine price for cost-effectiveness • Costs considered and data sources for costs not described
Graham (2015);[28] Canada	• Study objectives, rationale, viewpoint and design reported clearly • Data sources described and referenced • Model(s) described in detail	• Methods for valuation of benefits not explicitly described • Indirect benefits not addressed explicitly • Consideration of inflation not reported • Methods for handling stochastic data not detailed • Justification for selection of variables in sensitivity analyses not detailed
Haeussler (2015);[26] Italy	• Study objectives, rationale, and design reported clearly • Data sources described and referenced • Model(s) described in detail	• Analytical viewpoint not explicitly stated • Outcome(s) not explicitly described • Details re. inflation or currency conversion not explicit • Methods for handling stochastic data not detailed • Justification for selection of variables in sensitivity analyses not detailed

Table 8: Critical Appraisal of Included Guidelines

First Author, Year	Strengths	Limitations
US Advisory Committee on Immunization Practices (ACIP), December 2016[9] (Meites et al.)	• Objectives, clinical questions, and patient population defined or implied. • Guideline development group described. • Methods for searching for, selecting and assessing evidence described, plus formulating recommendations (GRADE tools) • Recommendations clearly identifiable and specific.	• Patient groups or views not represented. • Strengths and limitations of included evidence not described. • No detail about health benefits, side effects, and risks. • No mention of guideline updating, tools for application, barriers to adoption, costs, or monitoring. • Unclear whether externally reviewed.
National Advisory Committee on Immunization, July 2016[10]	• Objectives, clinical questions, and patient population defined or implied. • Methods for searching for and selecting evidence described. • Recommendations clearly identifiable and specific. • COI policy described.	• No mention of guideline updating, tools for application, barriers to adoption, costs, or monitoring. • Patient groups or views not represented. • No detail about health benefits, side effects, and risks. (Costs specifically excluded.) • Unclear whether externally reviewed.
Public Health Ontario: Provincial Infectious Diseases Advisory Committee, April 2015[29]	• Objectives, clinical questions, and patient population defined or implied. • Guideline development group described. • Recommendations clearly identifiable and specific. • Considers implementation issues in Ontario	• Strengths and limitations of included evidence not described (although adapted from NACI work). • No detail about health benefits, side effects, and risks. • Patient groups or views not represented. • No mention of guideline updating, tools for application, or monitoring. • Unclear whether externally reviewed.

COI = conflict of interest; NACI = National Advisory Committee on Immunization

Appendix 4: Main Study Findings and Author's Conclusions

Table 9: Summary of Findings of 4V Vaccine Studies

Main Study Findings	Authors' Conclusions
4V in teens and pre-teens (ages 9 to 15): Ferris et al. (2014)[6]	
At 8 years follow-up, no males (or females) who received the vaccine at mean age 12 developed HPV6/11/16/18-related disease or persistent infection of >12 months' duration. Subjects receiving vaccine at month 30 (mean age 15 years; CVG) had a similar baseline rate of seropositivity to those vaccinated at day 1 (mean age 12 years); however, 1 of the 90 males vaccinated at the later age was seropositive to 1 virus type, indicating pre-vaccine HPV exposure.	When administered to adolescents, the 4V vaccine demonstrated durability in clinically effective protection and sustained antibody titers over 8 years. No new significant serious adverse events were observed for 8 years after vaccination in both genders.
4V in men (ages 27 to 45): Giuliano et al. (2015)[4]	
The vaccine was generally well-tolerated and all men seroconverted to each of the four HPV vaccine components. Antibody responses did not differ by age group or sexual orientation	The immune response to HPV vaccination in men ages 27 to 45 years was comparable to that observed in younger men in whom clinical efficacy was demonstrated.
4V in men (ages 27 to 45): Swedish et al. (2014)[18]	
Among vaccinated patients, 10 developed anal warts during about 270 person-years of follow-up for an incidence rate of 3.7 per 100 person-years (95% CI 1.8 - 6.8/100 person-years). Among those who were not vaccinated, 37 developed anal warts during 504 person-years of follow-up for an incidence rate of 7.3 per 100 person-years (95% CI 5.2 to 10.1/100 person-years) (p = 0.05).	HPV vaccine decreases risk of anal condyloma among older MSM (ages 27 to 45). If results are confirmed by an RCT, the age of the vaccine's target population should be expanded over age 26, especially in high-risk populations like MSM.

CI = confidence interval; CVG = catch-up virus group; HPV = human papilloma virus; MSM = men who have sex with men; RCT = randomized controlled trial

Table 10: Summary of Findings of 9V Vaccine Studies

Main Study Findings for Males	Authors' Conclusions
9V in teens and pre-teens (ages 9 to 15): Iverson et al. (2016)[19]	
At 4 weeks after the last dose, HPV antibody responses in boys (and girls) given 2 vaccine doses were non-inferior to HPV antibody responses in females aged 16 to 26 who were given 3 doses (p<0.001 for each HPV type). In boys in particular, seroconversion rates at 6 months were essentially 100% (100% for eight HPV types and 99.3% for HPV-45).	For boys (and girls) aged 9 to 14 years who received 2-dose regimens, immunogenicity a month after the last dose was non-inferior to that of the young women (age 16 to 26) who received a 3-dose vaccine regime.
9V in teens and pre-teens (ages 9 to 15): van Damme et al. (2015)[20]	
At 4 weeks after dose 3, 100% of boys seroconverted for each vaccine HPV type. Increases in geometric mean titers to HPV types 6/11/16/18/ 31/33/45/52/58 were elicited in all vaccine groups. Responses in boys were non-inferior to those of young women aged 16 to 26. Persistence of anti-HPV responses was demonstrated through 2.5 years after dose 3.	The data support implementing gender neutral HPV vaccination programs in preadolescents and adolescents.
9V in men (ages 16 to 26): van Damme et al. (2016)[21]	
Anti-HPV antibodies to the 4 HPV types in the 4V vaccine (6, 11, 16 and 18) that were elicited by the 2 vaccines were not significantly different between groups. Exceptions were 7 men who did not seroconvert to HPV 6 and 2 men who did not seroconvert to HPV 18, rates that were similar between vaccines. Marked responses to the 5 additional HPV types covered by the 9V vaccine were measured post-dose 3 in the 9V vaccine with 100% of men seroconverting.	A 3-dose regimen of 9V vaccine elicited a similar antibody response to HPV 6/11/16/18 as did a 3-dose regimen of the 4V vaccine in men aged 16 to 26 years. Safety and tolerability were generally similar. Based on these results, the efficacy of 9V is inferred to be comparable to that found with 4V.

Table 10: Summary of Findings of 9V Vaccine Studies

Main Study Findings for Males	Authors' Conclusions
9V in men (ages 16 to 26): Castellsagué et al. (2015)[1]	
GMTs for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 for heterosexual men were non-inferior to those of women at Month 7. For all vaccine HPV types, Month 7 GMTs were numerically lower in MSM than in HM. Over 99.5% of subjects were seropositive at Month 7 for each vaccine HPV type .Administration of 9vHPV vaccine was generally well tolerated.	The study results support bridging the efficacy findings with 9V vaccine in young women ages 16 to 26 years to men in the same age group.

GMT = geometric mean titre; HPV = human papilloma virus; MSM = men who have sex with men

Table 11: Summary of the Findings of the Economic Analyses

Main Study Findings	Authors' Conclusions
Systematic reviews	
Sinisgalli (2015);[22] Italy	
Of the 15 included studies, expanding HPV vaccination to boys was cost-effective in 53%. Expansion of vaccination to boys was potentially cost-effective in 7% of studies. When analyses were adjusted for a two-dose schedule or costs of vaccines were lowered, all analyses demonstrated cost-effectiveness or potential cost-effectiveness.	"universal HPV vaccination program could greatly reduce the incidence of new HPV infections in the population, and is likely to be cost-effective and economically sustainable, considering current vaccine prices and the two-dose schedule"[22] (p. 57)
Yahia (2015);[23] France	
The systematic review identified 17 economic studies, 14 of which addressed the question of cost-effectiveness in men. Generally, extending vaccination to men was not found to be cost-effective when only considering the health outcomes for which HPV vaccines are licensed. However, when all HPV-related disease are considered, coverage for females is low (<40%), or reduced price (<USD$75) extending HPV vaccination to males may be cost-effective.	"Targeted vaccination of men who have sex with men (MSM) seems to be the best cost-effectiveness option. The feasibility of this strategy is still an open question, since early identification of this specific population remains difficult."[23] (p. 471)
Primary Analyses	
Brisson (2016);[3] USA	
Switching to 9V vaccination would lead to substantial reductions in cervical lesions and cancers, and cost savings in managing cervical lesions would be greater than the additional costs of the 9V program. Vaccinating girls with 9V provides the majority of cost-savings and QALYs gained of a 9V gender-neutral program.	Switching to 9V in a gender-neutral HPV vaccination program is likely to be cost-saving if the additional 9V cost/dose (versus 4V) is less than $13. Giving females 9V provides the majority of benefits of a gender neutral strategy.
Lin (2016);[24] UK	
Offering vaccination to HIV-positive MSM up to age 40 can be cost effective if vaccine costs (including administration) are under £96.50 a dose. At £48 a dose, this vaccination paradigm is likely to be cost-effective. Decreases in anogenital warts and male HPV-related cancer would be expected to follow.	Genitourinary clinic-based HPV vaccination for MSM was cost-effective with large impact on disease incidence, but the largest reductions in HPV-related disease occur through universal vaccination of boys age 12 to 13 because many MSM initiate same-sex activity before attending such clinics. Introducing gender-neutral vaccination does not preclude offering vaccination to MSM up to a higher age, particularly for males missed by an adolescent vaccination program.
Parada (2016);[25] Chile	
The outcome of interest was anal cancer. The estimated ICER was US $138,269/DALY (95% CI $95,936 to $221,862). Assuming a threshold of three times the per capita GDP, the intervention was not cost-effective. The outcome was sensitive to vaccine price and efficacy.	This study from Chile found that HPV vaccination of HIV-positive men was not cost-effective.

Table 11: Summary of the Findings of the Economic Analyses

Main Study Findings	Authors' Conclusions
Bogaards (2015);[30] Netherlands	
37% reduction in vaccine-preventable HPV cancers if girls' vaccine uptake is 60% (current level). To prevent one cancer among men, 795 boys would need to be vaccinated. 66% reduction if girls' vaccine uptake was 90%. To prevent one cancer among men, 1735 boys would need to be vaccinated. "if the net costs exceed €100 (£72; $107) per vaccinated boy, sex neutral vaccination is unlikely to be economically feasible." (p. 7)	Men will benefit indirectly from vaccination of girls but remain at risk of cancers associated with HPV. The incremental benefit of vaccinating boys when vaccine uptake among girls is high occurs because of the prevention of anal carcinomas in men, this particularly justifies HPV prevention efforts for MSM. "a cost effective implementation of sex neutral vaccination requires low vaccine pricing" (p. 1)
Graham (2015);[28] Canada	
Versus no vaccine: • Vaccination produced 0.05 more QALYs and saved CAD $145 Canadian per person, assuming 99% vaccine efficacy and 70% uptake • Vaccination produced 0.023 more QALYs and saved CAD $42 per person, assuming 50% vaccine efficacy and 50% uptake.	V4 vaccination in males may save CAD $8 million to $28 million for a theoretical cohort of Canadian males age 12 in Canada in 2015 (n=192,940) over the cohort's lifetime. HPV vaccination for boys aged 12 years may be a cost-effective strategy for the prevention of oropharyngeal cancer in Canada.
Haeussler (2015);[26] Italy	
Universal vaccination resulted in an ICER of €1,500 when compared with cervical cancer screening alone. Universal vaccination was cost-effective with an ICER of €11,600 when compared with female-only vaccination.	In Italy, universal HPV vaccination was found to be cost-effective versus either cervical cancer screening or female-only vaccination. With the introduction of 9V vaccine, the cost effectiveness of universal HPV vaccination is likely to further improve, creating added potential to optimize control of the disease.

CI = confidence interval; CIN = cervical intraepithelial neoplasia; DALY = disability-adjusted life-year; GDP = gross domestic product; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life-year; UI = uncertainty interval

Table 12: Summary of the Recommendations of the Clinical Guidelines

US Advisory Committee on Immunization Practices (ACIP), December 2016[9] (Meites et al 2016)
NOTE: There was no specific mention of 4V versus 9V (only 9V is available in the US at present). • 2-dose schedule (second dose 6 to 12 months after the first) for girls and boys who initiate the vaccination series at ages 9 through 14 years (preference for age 11 or 12 but age 9 if a history of sexual abuse or assault). • 3-dose schedule for females through age 26 years and males through age 21 years who were not previously vaccinated if starting the series at age 15+ (0, 1, 6 month schedule). Males aged 22 through 26 years may be vaccinated, particularly MSM and transgender persons. • 3-dose schedule for females and males aged 9 through 26 years with primary or secondary immunocompromising conditions that might reduce cell-mediated or humoral immunity (e.g., B lymphocyte antibody deficiencies, T lymphocyte complete or partial defects, HIV infection, malignant neoplasms, transplantation, autoimmune disease, or immunosuppressive therapy).
National Advisory Committee on Immunization (Public Health Agency of Canada), July 2016[10]
• V4 and V9 vaccines (Gardasil) are indicated in all males 9 to 26 years of age for the prevention of anal cancers, pre-cancerous lesions and anogenital warts. They may be used in males over 26 years of age who have not been vaccinated previously or who have not completed the series. • A 2-dose or 3-dose series may be used for V4 but there is not enough evidence to drop to a 2-dose regimen for V9. • A 3-dose series is recommended for individuals: (a) who are immunocompromised, (b) who are HIV positive and immunocompetent, and (c) who have not had any HPV vaccine by age 15. • At a population level, there is insufficient evidence to recommend re-immunization with V9 vaccine in individuals who have completed an immunization series with another HPV vaccine.
Public Health Ontario (2015)[29]
A 3-dose schedule of the 4V vaccine is recommended for individuals who are immunocompromised and immunocompetent HIV-infected individuals. (The guideline otherwise does not mention males as candidates for HPV immunization.)

MSM = men who have sex with men