A Review of the Impact and Effectiveness of the Quadrivalent Human Papillomavirus Vaccine: 10 Years of Clinical Experience in Canada

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Abstract

Publicly funded administration of the quadrivalent HPV (qHPV) vaccine in school-aged girls was implemented for all Canadian provinces and territories between 2007 and 2009. However, the impact of female qHPV vaccination in Canada has yet to be evaluated. This systematic literature review of studies published between September 1, 2006 and September 1, 2016 looked at real-world evidence related to the effects of qHPV vaccination on prevalence of HPV infection and disease in Canada over the past decade. PubMed was searched for studies published between September 1, 2006 and September 1, 2016. Studies were eligible if one or more of the following outcomes were assessed in individuals receiving the qHPV vaccine though public immunization programs: HPV infection, anogenital warts (AGW), HPV-associated lesions of the anogenital tract. A "pre-public vaccination program" or "unvaccinated" reference group was required. Key HPV conference abstracts were also reviewed. We identified seven eligible studies representing five Canadian provinces. Results reported indicated that the prevalence of HPV types 6, 11, 16, and 18 was lower in qHPV-vaccinated than unvaccinated individuals (1.5% vs. 11.0%, respectively), whereas non–vaccine-covered genotypes were comparable across vaccination status. Risk of AGW incidence decreased by up to 45% in vaccinated cohorts; incidence of cervical intraepithelial neoplasia 2 + was significantly reduced by up to 86% in the post-vaccine era. On the basis of these findings, HPV vaccination programs constitute a successful and effective public health initiative.

Key Words: Papillomavirus infections, papillomavirus vaccines, immunization programs, Canada, public health, females

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Competing interests: See Acknowledgements.

Received on March 7, 2018

Accepted on May 16, 2018

Résumé

L'administration financée par l'État du vaccin quadrivalent contre le VPH (VPH-4) chez les filles d'âge scolaire a été mise en œuvre dans toutes les provinces et tous les territoires du Canada entre 2007 et 2009. Cependant, l'incidence de cette mesure n'a pas encore été évaluée. Cette revue systématique s'est penchée sur les données concrètes associées aux effets de la vaccination au VPH-4 sur la prévalence de l'infection au VPH et des maladies connexes au Canada au cours des 10 dernières années. Nous avons interrogé PubMed pour trouver les études publiées entre le 1er septembre 2006 et le 1er septembre 2016, et avons retenu celles évaluant au moins une des issues suivantes chez les personnes ayant reçu le vaccin VPH-4 dans le cadre d'un programme public : infection au VPH, verrues dans la région anogénitale, lésions de la région anogénitale associées au VPH. Un groupe témoin « avant vaccination publique » ou « non vacciné » était requis. Des résumés de congrès majeurs sur le VPH ont aussi été examinés. Nous avons relevé sept études admissibles représentant cinq provinces canadiennes. Les résultats rapportés indiquaient que la prévalence du VPH 6, 11, 16 ou 18 était plus faible chez les personnes vaccinées au VPH-4 que chez les personnes non vaccinées (1,5 % contre 11,0 %, respectivement), alors que les taux d'infection aux génotypes non couverts par le vaccin étaient comparables dans les deux groupes. Nous avons constaté une diminution de l'incidence de verrues dans la région anogénitale allant jusqu'à 45 % chez les cohortes vaccinées; de même, l'incidence de néoplasie intraépithéliale cervicale de grade 2 ou plus a diminué de façon significative (jusqu'à 86 %) après le début de la vaccination. Il semblerait donc que les programmes de vaccination contre le VPH constituent une initiative efficace de santé publique.

J Obstet Gynaecol Can 2018;40(12):1635–1645

https://doi.org/10.1016/j.jogc.2018.05.024

INTRODUCTION

HPV is a highly infectious virus transmitted through oral, anal, or genital sexual contact, as well as through non-penetrative sex involving skin-to-skin contact.[1,2] Ubiquitous in sexually active individuals, HPV is capable of infecting cells of the skin or mucous membranes of the oral cavity, respiratory tract, or anogenital epithelium.[3–5] Given the asymptomatic and self-limiting nature of HPV infections, most carriers remain unaware of their positive status because over 90% of infections are spontaneously cleared within 2 years.[6] It is estimated that 80% of sexually active individuals will have at least one HPV infection during their lifetime.[7]

Of the 120 HPV genotypes identified, 40 are capable of infecting the anogenital tract and are categorized into low and high risk on the basis of their capacity to induce malignancy.[2,8–10] Low-risk (LR) genotypes, such as HPV-6 and HPV-11, are associated with non-malignant manifestations of infection such as anogenital warts, low-grade squamous intraepithelial lesions, and recurrent respiratory papillomatosis.[11] Most cases of external genital warts and recurrent respiratory papillomatosis are caused by infection with HPV and in at least 90% of cases, HPV-6 or HPV-11 are the causative factors.[12,13] Although LR HPV genotypes rarely progress to malignancy, they have been identified as a minor risk factor for the development of anogenital cancer,[11,14] and they are associated with important morbidity, high psychosocial impact, and costly treatment.[15] In addition, 13 HPV genotypes are categorized as high-risk (HR) because of their etiologic contribution to the development of cervical or other genital cancers.[9,16] The most potent of these HR genotypes are HPV-16 and HPV-18, which together are responsible for over 70% of all cervical cancers worldwide, the prevalence of which varies by region.[9]

In Canada, the quadrivalent HPV vaccine was licensed for use in 2006.[17] All provinces and territories now publicly fund the HPV vaccine for school-aged adolescent girls and boys, although age of administration is province or territory dependent. Implementation of publicly funded HPV programs for school-aged girls between the ages of 9 and 14 in Canada spanned from 2007 to 2010.[18] Implementation of publicly funded HPV programs for boys in Canada started in 2013 with Prince Edward Island and gradually expanded to the other provinces and territories over the years, with the most recent programs starting in September 2017.[19] The various HPV vaccination programs for school-aged adolescents over the past 10 years have had a noticeable impact on the rate of HPV-related diseases nationwide, albeit to varying degrees of success, depending on vaccine uptake rates. Immunization rates within these public HPV immunization programs vary from 39.3% to 93.0% across provinces and territories.[18] Although several systematic reviews have ascertained the real-world impact of qHPV vaccination globally,[20–23] a comprehensive assessment of the impact and effectiveness of publicly funded HPV vaccination in Canada has yet to be performed.

The purpose of this systematic review is to summarize available Canadian data assessing the real-world impact of 10 years of publicly funded qHPV vaccination on rates of HPV-6, HPV-11, HPV-16, and HPV-18 infection, genital warts, and precancerous lesions.

ABBREVIATIONS

AGW	anogenital wart
aOR	adjusted OR
CIN	cervical intraepithelial neoplasia
HR	high-risk (genotype)
IRR	incidence rate ratio
qHPV	quadrivalent HPV (vaccine)
RR	relative risk

METHODS

Search Strategy and Selection Criteria

The PubMed database was searched for studies published between September 1, 2006 and September 1, 2016 to select studies assessing the impact of the qHPV vaccine in Canada. The PubMed search strategy is provided in the online Appendix.

HPV conference abstracts and peer-reviewed publications were reviewed to evaluate whether the study populations assessed included vaccination though public immunization programs. Eligible studies and abstracts include those that reported at least one of the following outcomes assessed in post-qHPV vaccination program era: HPV infection, HPV-associated AGW, and/or HPV-associated cervical dysplasia or cervical intraepithelial neoplasia. A "pre-public vaccination program" or "unvaccinated" reference group was required to ascertain the impact of qHPV vaccination. Studies were excluded if they were controlled clinical trials or if the study population studied received the qHPV vaccine through private insurance or out-of-pocket payment. Review articles were not permitted, but references lists were examined for articles not identified previously. Two independent reviewers assessed all records for eligibility. Corresponding authors of all included records were contacted to validate presentation and interpretation of data. Levels of evidence were rated using the ranking of the Canadian Task Force on Preventive Health Care.[24] Because this review was

intended to be purely descriptive, statistical heterogeneity among the studies was not assessed.

RESULTS

Search Results

A detailed search flow diagram is provided in Figure 1, and the records included in the present review are described in the Table 1. Overall, 196 publications were identified from the PubMed database search. In addition, four conference abstracts and one provincial study report were found in grey literature, for a total of 201 records. After the removal of duplicates (n = 1), initial screening, and in-depth review of full-length publications, a total of 193 records were deemed ineligible, resulting in seven studies included in the current review. These consisted of four peer-reviewed publications, two conference abstracts, and one provincial public health study report. Three records provided level II-2 evidence (evidence from a well-designed cohort or case-control study), with the remaining four providing level II-3 evidence (evidence obtained from comparisons between times or places with or without the intervention).

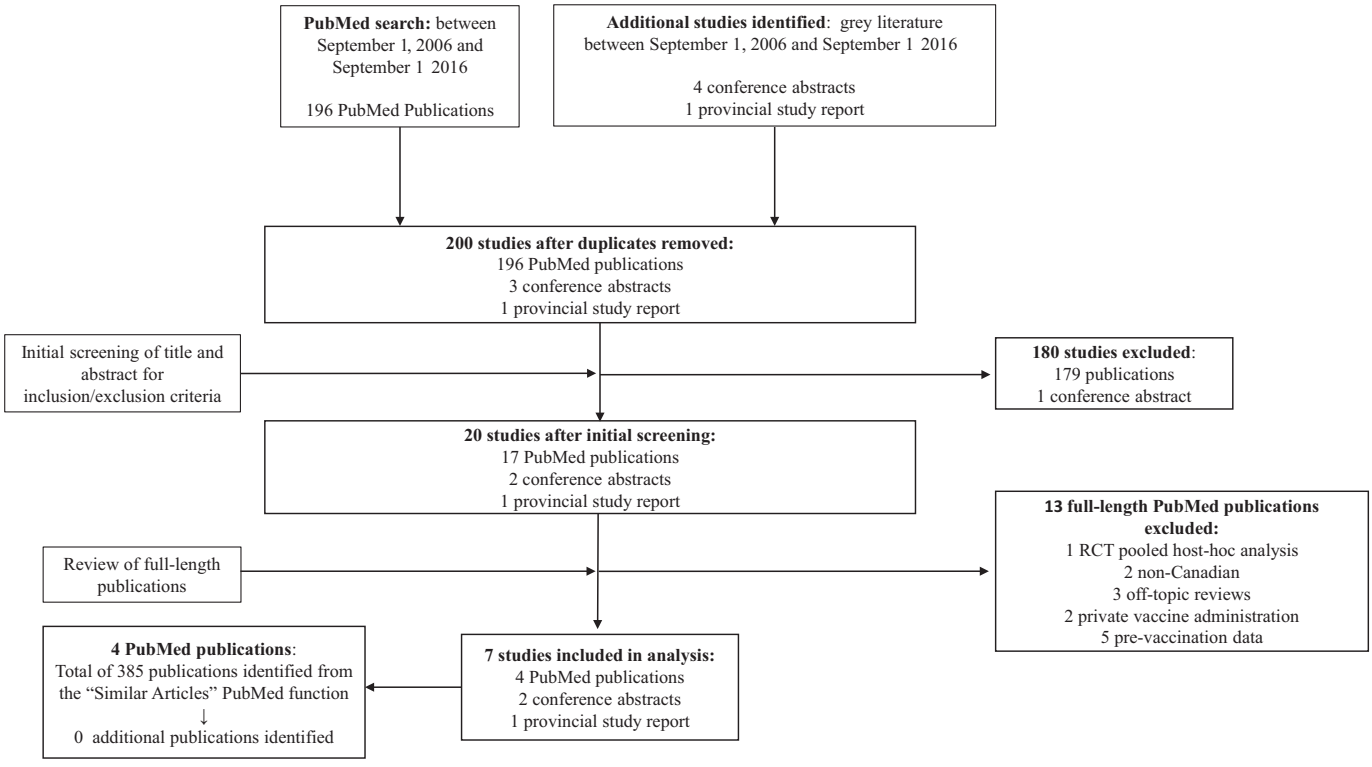
Overall, five Canadian provinces were represented across the seven eligible records: Québec (n = 2), Ontario (n = 2), Manitoba (n = 1), Alberta (n = 1), and British Columbia (n = 1). No Canadian territory had published an evaluation record in the described time period.

Study Characteristics and Outcomes

Impact on HPV prevalence

Québec. In Québec, a public school–based qHPV vaccine program was introduced in September 2008 for girls aged 9 to 17. The impact of qHPV vaccination on the prevalence of HPV infection was investigated by the Institut national de santé publique du Québec (INSPQ),[25] whereby the "PIXEL- Portrait de la santé sexuelle des jeunes adultes au Québec" study recruited female participants aged 17 to 29 who were asked to provide a vaginal sample for HPV testing and genotyping. The qHPV vaccination status of participants was also ascertained (level II-2). Overall HPV prevalence was significantly higher in non-vaccinated women than in vaccinated women (47.2% vs. 36.1%, $P < 0.001$) (Figure 2). This difference in HPV prevalence was most evident for genotypes covered by the qHPV vaccine:

Figure 1. Search flow diagram.



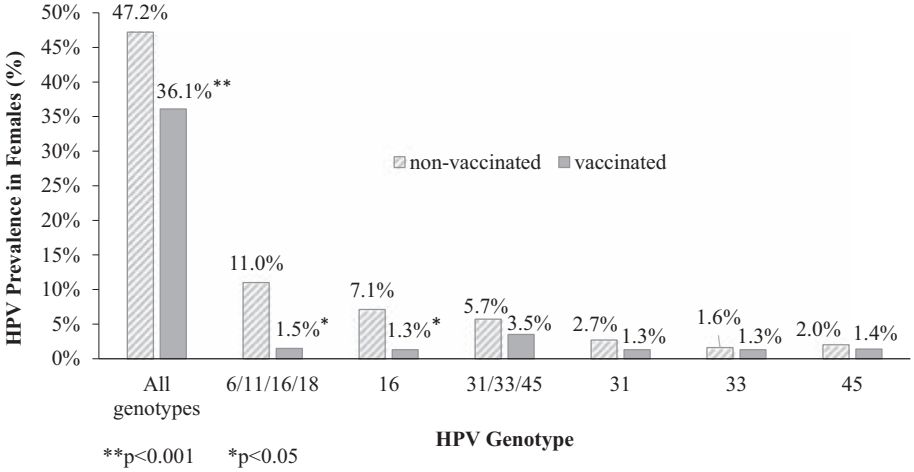
Flow diagram indicates search parameters and study criteria to qualify for inclusion in the present review. Studies were categorized according to study design. A total of 196 articles, three abstracts, and one report were identified within the selected search period. Following screening of all articles according to the predetermined measures, a total of seven publications—four Medline publications, two abstracts, and one report—were included in the final analysis.

Table 1. Characteristics of records included in the review

Record	Publication	Level of evidence[a]	Outcome	Province or territory	Study design and data sources	Target population	Endpoint and measure of effect	Estimated qHPV vaccine coverage
1	Institut national de santé publique du Québec (INSPQ), 2016[25]	II-2	HPV infection	Québec	Prospective, population-based survey; questionnaire and vaginal self-samples	Girls and women aged 17–29; between March 2013 and July 2014	Prevalence of HPV infection by genotype and by vaccination status; proportion	62.3% overall 83.5%: aged 17–19 65.7%: aged 20–22 19.1%: aged 23–23
2	Steben et al. 2014[26]; Steben et al. 2018[27]	II-3	AGWs	Québec	Retrospective longitudinal study; administrative health database	Girls aged ≥9–14 Time periods: pre-vaccine program (2004–2007); post-vaccine program (2009–2012)	Pre- vs. post vaccine program incidence rates of AGWs; proportion	81% girls grade 4; 84% girls grade 9 (2012–2013)
3	Willows et al., 2016[30]	II-2	AGWs	Manitoba	Retrospective, historical matched cohort study; vaccine registry	Girls aged ≥9 vaccinated between September 2006 and March 2013; matched to three unvaccinated girls on the basis of age and area of residence	Development of AGWs by vaccination status; hazard ratio	65% in 2009 to 72% in 2012
4	Guerra et al., 2016[28]	II-3	AGWs	Ontario	Retrospective longitudinal study; administrative health database	Girls and women aged 15 older. Time periods: pre-vaccine program (2004–2007); post-vaccine program (2008–2014)	Pre- vs. post vaccine program incidence rates of AGWs; proportion	51% in 2007–2008 to 80% in 2012-2013[49]
5	Smith et al., 2015[29]	II-3	AGWs and cervical dysplasia	Ontario	Retrospective cohort study; administrative health database	Girls in grade 8 pre-vaccine program (2005–2006–2006–2007) and post-vaccine program (2007–2008–2008–2009)	Incidence rates of AGWs and cervical dysplasia in pre- vs. post vaccine program cohorts; RR	59 % for three doses with extended eligibility from grade 8 to grade 9 in 2008-2010[45]
6	Kim et al. 2016[31]	II-2	Cervical abnormalities	Alberta	Nested case-control study; provincial repositories of vaccination status and Pap test results	Women born between 1994 and 1997, who had at least one Pap test between 2012 and 2015	Incidence rates of cervical dysplasia by vaccination status; OR	44 % had at least one dose of the qHPV vaccine
7	Ogilvie et al., 2015[32]	II-3	CIN	British Colombia	Retrospective, population-based study; provincial cervical cancer program database	Girls and women aged 15–22 between 2004 and 2012. Time periods: pre-vaccine program (2004–2009); post-vaccine program (2010–2012)	Pre- vs. post-vaccine program incidence rates of CIN; IRR	58.1% and 61.7% per year from Sept 2009–2010 (grade 9)

[a]Rated using the ranking of the Canadian Task Force on Preventive Health Care[22]. II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group; II-3: evidence obtained from comparisons between times or places with or without the intervention.

Figure 2. HPV prevalence (%) in 17- to 29-year-old girls and women living in Québec. Prevalence of HPV (%) reported for the female-only vaccination era, as reported by the Institut national de santé publique du Québec (PIXEL study).[25]



prevalence of HPV-16 was significantly higher in non-vaccinated than in vaccinated individuals (7.1% vs. 1.3%, $P < 0.05$), as was the cumulative prevalence of HPV-6, HPV-11, HPV-16, and HPV-18 (11.0% vs. 1.5%, $P < 0.05$). Prevalence rates of oncogenic and non-oncogenic HPV genotypes not contained within the qHPV vaccine were not found to be significantly different between vaccinated and unvaccinated women (Figure 2).

Anogenital warts

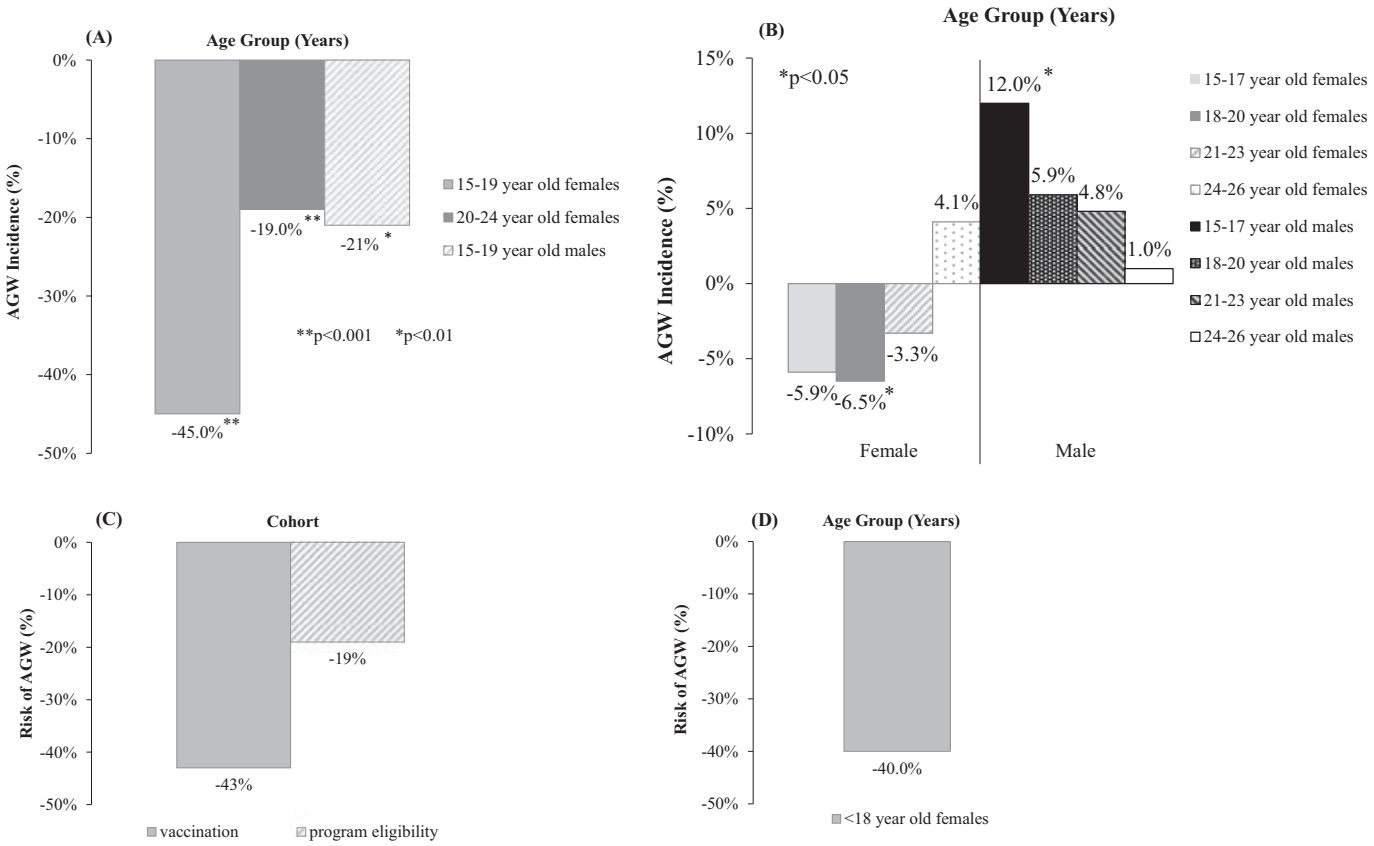
Four retrospective, administrative health database or registry studies evaluated the impact of the qHPV vaccination on the incidence of AGW.

Québec. A study by Steben et al. estimated the impact of HPV vaccination on the incidence rates of AGWs in the publicly insured population during the pre-vaccine (2004–2007) and qHPV vaccine (2009–2012) periods[26] in Québec (level II-3). AGWs were identified using the linkage of the physician service claims and the public drug plan database (RAMQ), the latter covering 41% of the population. Although individual vaccination status is not known, results indicate a significant decline of 45% ($P < 0.0001$) and 19% ($P < 0.0001$) in the incidence rate of AGWs among girls and women aged 15 to 19 and 20 to 24, respectively (Figure 3A). A smaller change was observed in women aged ≥25. Moreover, a small but significant decline of 21% ($P = 0.004$) was also seen in boys and young men aged 15 to 19, but not in older men. Interestingly, in women, the median age at an episode of AGW increased from 27 years in 2004 to 31 years in 2012, but it remained stable in men. An abstract of this study was presented in 2014, and final publication is now available.[27]

Ontario. Ontario's school-based qHPV vaccination program was implemented in September 2007 for grade 8 girls. A retrospective longitudinal study by Guerra et al.[28] assessed the impact of HPV vaccination on AGW rates before and after vaccine program implementation in Ontario residents aged 15 to 26 (level II-3). This study did not assess individual-level data on vaccination status, but rather it assessed the trends at a population level using the Ontario Health Insurance Plan database, which captures approximately 90% of AGW health service visits occurring within institutions reporting data to the provincial health insurance administrative datasets. The incidence of AGW was adjusted for the impact of changes in Pap testing rates resulting from revisions to Ontario's cervical screening guidelines in 2011 and associated changes to Ontario Health Insurance Plan Pap testing reimbursement for physicians in 2012 (Pap test–adjusted incidence). From the pre-vaccine era (2004–2007) to the vaccine rea (2008–2014), Pap test–adjusted AGW incidence decreased significantly by .5% ($P = 0.03$) in 18- to 20-year-old women, decreased non-significantly in 15- to 17-year-old girls and 21- to 23-year-old women, and increased non-significantly by 4.1% among 24- to 6-year-old women (Figure 3B). Between the pre-vaccine and vaccine eras, AGW incidence increased significantly by 12% in 15- to 17-year-old boys ($P = 0.04$) and increased non-significantly in 18- to 20-, 21- to 23-, and 24- to 26-year-old men.

A separate publication by Smith et al.[29] estimated absolute risk differences and relative risks attributable to vaccination and program eligibility in a cohort of grade 8 girls in Ontario before (2005–2006–2006–2007) and after (2007–2008–2008–2009) program implementation (level II-3). Vaccine exposure was determined in grades 8 to 9, and

Figure 3. Changes in AGW incidence (%) during the female-only vaccination era in Canada.



(A) AGW incidence between pre-vaccine and vaccine periods in individuals living in Québec, as reported by Steben et al.[26] (B) Pap test–adjusted AGW incidence rates in girls and women and AGW incidence rates in boys and men living in Ontario, as reported by Guerra et al.[28] An AGW incidence rate is compared between the pre-vaccine and vaccine eras. (C) Smith et al.[29] estimated the impact of vaccination and program eligibility on the risk of AGWs in girls aged 14 to 17 and living in Ontario. The programeligible group includes girls who are eligible for the public program, regardless of vaccination status. Results suggest decreases in detected AGW as a result of program eligibility and vaccination, even though the results are not statistically significant. (D) AGW incidence in vaccinated girls aged ≥9 and living in Manitoba.

outcomes were ascertained in grades 10 to 12. The impact of the qHPV vaccine on AGWs was estimated in two populations: (1) subjects who received the qHPV vaccine (vaccine impact); and (2) subjects who are eligible for qHPV vaccination, regardless of vaccine receipt (program impact). Results suggested a reduction in AGW by 43% (RR 0.57, 95% CI 0.20–1.58) as a result of vaccination and by 19% (RR 0.81, 95% CI 0.52–1.25) as a result of vaccine program eligibility (Figure 3C). However, these results were not statistically significant.

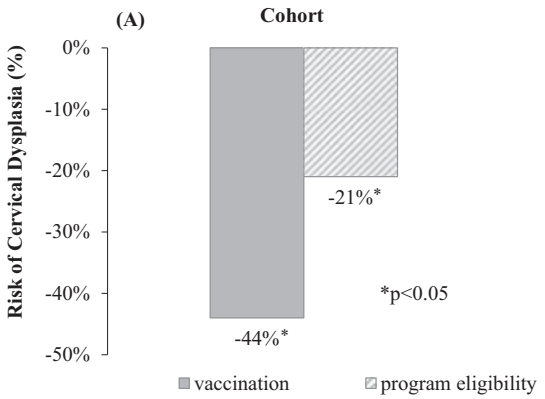
Manitoba. Manitoba's school-based qHPV vaccination program was implemented in September 2008 for grade 6 girls. In this study, Willows et al.[30] assessed the vaccine efficacy in qHPV-vaccinated versus unvaccinated girls aged ≥9 in Manitoba (level II-2). Results found a 40% reduction in AGW risk for girls and women vaccinated before the age of 18 (hazard ratio 0.6, 95% CI 0.4–0.8) (Figure 3D). Among girls vaccinated at age >18, the qHPV vaccine was associated with increased AGW risk, especially among those who were sexually active (hazard ratio 2.8, 95% CI 2.1–3.7), likely as a result of increased qHPV vaccine use among high-risk women. Women currently infected with HPV may not be fully protected by qHPV vaccination because the vaccine is not therapeutic.

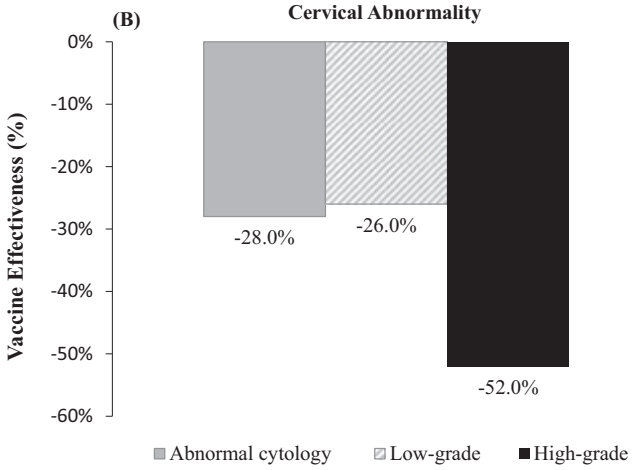
Cervical abnormality and cervical intraepithelial neoplasia

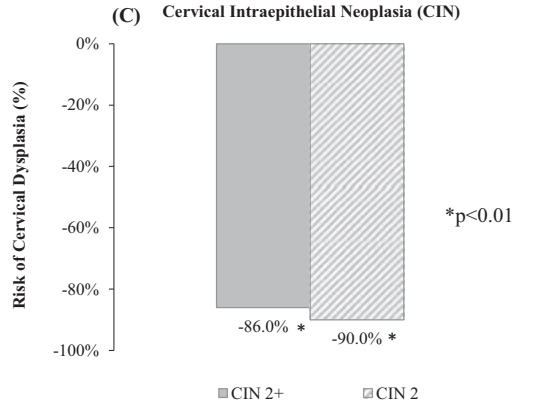
Ontario. In addition to studying the incidence of AGWs in Ontario, Smith et al.[29] also evaluated the impact of qHPV vaccination on cervical dysplasia (level II-3). Vaccination significantly reduced the incidence of dysplasia by 44% (RR 0.56, 95% CI 0.37–0.87). Vaccine program eligibility also had a significant protective effect on dysplasia with an RR reduction of 21% (RR 0.79, 95% CI 0.66–0.94) (Figure 4A).

Alberta. Alberta's school-based qHPV vaccination program was implemented in September 2008. Kim et al.[31] measured the impact of qHPV vaccination on cervical

Figure 4. Changes in risk for cervical abnormalities during the female-only vaccination era in Canada.







Histopathology abnormalities of CIN 2 and CIN 2+ were selected as relevant endpoints as they are both correlated with the risk of progression to invasive cervical cancer. CIN nomenclature was used in this analysis because at the time of screening it was the histopathological nomenclature used by pathologists in British Columbia.

ASC-US = atypical squamous cells of undetermined significance.

ASC-H = atypical squamous cells, cannot rule out a high-grade lesion.

Abnormal cytology: Atypical squamous ASC-US, LSIL, ASC-H or HSIL.

Low-grade: ASC-US or LSIL.

High-grade: ASC-H or HSIL.

Control: negative cytology result.

(A) Estimated impact of vaccination and program eligibility on risk of cervical dysplasia in girls aged 14 to 17 and living in Ontario, as reported by Smith et al.[29] (B) Cervical abnormalities in women who received full vaccination (three or more doses) compared with no vaccination. Vaccine effectiveness was calculated for abnormal cytology results, low-grade cervical abnormalities, and high-grade cervical abnormalities. Results were reported by Kim et al.[31] LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesions. (C) IRRs of CIN2+ and CIN2 in vaccine-eligible young women aged 15 to 17 before and after HPV vaccine introduction in British Columbia, as reported by Ogilvie et al.[32]

abnormalities in Albertan girls and women born between 1994 and 1997 who have had at least one Pap test performed between 2012 and 2015. Interestingly, vaccinated women were found to have significantly higher screening rates than unvaccinated women (13.0% vs. 11.4%, $P < 0.001$) when adjusted for age (level II-2).

Adjusted OR of cervical abnormalities were significantly lower in women who received three or more doses of the qHPV vaccine, with risk reduction of 28% (aOR 0.72, 95% CI 0.63–0.82), 26% (aOR 0.74, 95% CI 0.64–0.85), and 52% (aOR 0.48, 95% CI 0.28–0.81) for abnormal cytology, low-grade cervical abnormalities, and high-grade cervical abnormalities, respectively (Figure 4B). With two doses of qHPV vaccination, the aOR was 1.08 (95% CI 0.84–1.38), 1.15 (95% CI 0.90–1.49), and 0.17 (95% CI 0.02–1.20) for abnormal cytology, low-grade cervical abnormalities, and high-grade cervical abnormalities, respectively. qHPV vaccination was found to reduced high-grade cervical abnormalities on cytology significantly, but it required a three-dose schedule.

British Columbia. British Columbia launched its HPV vaccine program for grade 6 girls in September 2008, with

a 3-year catch-up program in grade 9 ending in June 2011. Ogilvie et al.[32] reported on the rates of CIN, as assessed by cytology, in young women aged 15 to 22 who were living in British Columbia (level II-3). The incidence rate ratios of CIN2+ were compared before and after the qHPV vaccine program introduction in both vaccine-eligible and non–vaccine-eligible cohorts. Since the introduction of the HPV vaccine program, the IRR for in young women aged 15 to 17 was significantly reduced by 86% for CIN2+ (IRR 0.14, 95% CI 0.04–0.47, $P < 0.01$) and 90% for CIN2 (IRR 0.1, 95% CI 0.02–0.54, $P < 0.01$) (Figure 4C). This significant decrease in CIN was seen in young women aged 15 to 17 (eligible to receive HPV vaccine), but no similar reduction was found in women aged 18 to 22 (vaccine-ineligible cohort).

DISCUSSION

The findings of a reduction in HPV-related infection and disease across Canada are consistent with clinical trials and provide evidence for the real-world effectiveness of the HPV vaccine at the population level. Decreases in HPV prevalence, AGWs, low- and high-grade CIN, and CIN2+ (CIN ≥grade 2) were observed in the post-vaccine era. In addition, these decreases were highest in the younger cohorts of girls, reflecting either a lower likelihood of prevalent HPV infection at the time of vaccination or a greater likelihood of vaccine uptake, thus potentially highlighting the benefits of younger age at vaccination.

All studies included varied with respect to study design, data source, and statistical methodology. Nevertheless, both Steben et al.[27] and Guerra et al.[28] reported significant reductions in the rate of AGW incidence in the post-vaccine program era. Although a two-fold higher reduction was reported by Steben et al. compared with Guerra et al. (45.0% vs. 18.6% to 21.2% in patients under age 20), differences in the time frame considered "post-vaccine" may have contributed to this discrepancy. Steben et al.[27] did not consider the year of vaccine program implementation in Québec (2008) in their definition of the post-vaccine era, whereas Guerra et al.[28] included the Ontario index year of publicly funded qHPV vaccination (also 2008) when assessing post-vaccine AGW incidence.

Two additional studies assessing AGWs, by Willows et al.[30] and Smith et al.[29], despite differences in statistical methodology (hazard ratio vs. RR, respectively) and reference group used (matched cohort vs. pre-vaccine program cohort, respectively), reported comparable results with respect to incidence of AGW, with an approximately 40.0% reduction in risk reported across both studies. Smith et al.,[29] however, did not report this reduction in AGW risk to be statistically significant; again, this may be attributed to a difference in time frame explored, as well as interprovincial differences in minimum age of qHPV eligibility at the time of study conduct. Although both studies assessed incident AGW to age 18, Willows et al.[30] included all girls aged ≥9 (eligibility in Manitoba as of grade 6), assessing outcomes from September 2006 to March 2013, whereas Smith et al.[29] assessed outcomes from grade 8 onwards (mean age of the cohort 13.17 years) within a more restricted study time frame (2005–2006 to 2008–2009). As such, the impact of qHPV on AGW may not have been fully apparent in the cohort studied by Smith et al.[29]

With respect to assessment of cervical outcomes, the studies by Kim et al.[31] and Smith et al.[29] also differed with respect to the reported point estimates (OR vs. RR) and reference group used (matched cohort vs. pre-vaccine), as well as with respect to endpoint assessed (general cervical dysplasia vs. high-grade abnormalities); however, similar significant reductions in incidence of cervical endpoints (44.0% vs. 50%, respectively) were observed. Although the study by Kim et al.[31] reported a lack of vaccine impact found for those vaccinated with two doses of the qHPV vaccine, within this publication, the median time interval between the first and second doses was shorter than the recommended interval of 6 months for pre-adolescents aged 9 to 13 by the WHO. The short interval between doses may result in low-affinity maturation of memory B cells affecting lasting immunity.[33]

Although most of the data summarized herein have been extracted from ecological studies providing indirect evidence of effectiveness, the PIXEL study provided results supporting a causal association between the reductions observed and qHPV vaccination. This study reported a significantly lower prevalence of genotypes covered by the qHPV in vaccinated girls and women compared with unvaccinated girls and women, with rates of non-qHPV covered genotypes comparable across vaccination status.[25]

Because of the proven safety and efficacy of prophylactic HPV vaccination in both controlled clinical trials and real-world studies, as reported herein, the HPV vaccine was incorporated into the routine immunization schedules of approximately 70 countries worldwide as of 2016.[20,22,23,33–37] In addition, numerous health and regulatory agencies, including the WHO,[38] the Food and Drug Administration,[39] the European Medicines Agency,[40] and Health Canada,[41] have independently reviewed and confirmed the safety of prophylactic HPV vaccines. The WHO further advocates for the instatement of nationwide immunization programs in all countries.[42]

In Canada, specifically, all provinces and territories have implemented organized school-based HPV immunization programs since 2010, although uptake varies from 47% in the North West Territories to 93% in Newfoundland for the first dose. In addition, on average, coverage for the HPV vaccine is lower than for the hepatitis B virus vaccine, although both viruses have similar risk profile, are sexually transmitted, and can lead to cancer.[43] Some studies suggest that barriers to uptake are the result of parent perception that vaccines are unsafe or that qHPV vaccination will encourage unprotected sexual activity, despite scientific evidence that suggests otherwise.[44] Data from Ontario provide strong evidence that HPV vaccination does not have any significant effect on clinical indicators of sexual behaviour among adolescent girls; no statistically significant increase in the risk of pregnancy and non–HPV-related sexually transmitted infections among girls aged 14 to 17 was observed as a result of HPV vaccination.[45]

With respect to study limitations, the observed differences in vaccine effectiveness across studies may be in part due to the variations in study design, specifically with respect to data sources, choice of reference group, and statistical methodology. In addition, a major shortcoming of the current review is the variability of populations studied with respect to geographic region, as HPV genotype distribution may vary geographically as well as socioeconomically, with greater prevalence of HR genotypes found in socially disadvantaged population subgroups.[46,47] Moreover, interprovincial differences in qHPV immunization programs with respect to operational differences, such as the timing of delivery and eligibility for coverage combined with variable rates of vaccine uptake,[18] have resulted in a heterogeneous pattern of vaccination that differs across provinces and varies by age, sex, and, in some cases, sexual orientation and immune status.[19] Nevertheless, on the basis of the results of this review, HPV vaccine effectiveness appears to be resistant to this heterogeneity, and vaccine-associated reduction in HPV-related infection and disease has been consistently observed across Canada.[18]

Regardless of study limitations, this is the first comprehensive assessment of the early benefits and impact of the qHPV vaccine in a Canadian real-world setting. Despite suboptimal vaccine uptake, the results of this review demonstrate a positive association between qHPV vaccination and reductions in the prevalence of vaccine-preventable HPV infections, as well as in the incidence of AGW, cervical abnormalities, and pre-cancer diagnostic events. Because measuring and reporting on HPV vaccination uptake help to inform opportunities for increased efforts in prevention activities,[44,48] these results are promising for regions of the world that have not yet implemented publicly funded HPV immunization programs.

Future studies will no doubt explore the impact of gender-neutral vaccination as results from Canadian provinces and territories become available. Furthermore, because of the natural history of HPV-related cancers, forthcoming data will delineate the impact of HPV vaccination on cancer incidence within the Canadian population.[47] Finally, with the recent introduction of the nine-valent HPV vaccine into the Canadian public health program, we will likely be able to assess incremental benefit and protection conferred by the nine-valent HPV vaccine in Canada within the next decade.

Acknowledgements

This work was supported by Merck Canada. The methodology and results of this systematic literature review, as well as the interpretations and conclusions presented herein, were developed and reached independent of the funding source. Ms. Rodier, Dr. Tan Thompson, Ms. Mallette, Ms. Racovitan, and Ms. DeAngelis are employees of Merck Canada. Dr. Steben reports grants, personal fees, and non-financial support from Merck outside the submitted work and has received research grants, lectures, and advisory board fees or support fees from Beckton-Dickinson, Cepheid, Hologic/Gen-Probe, Innovio, Merck/Merck Sharp Dohme/Sanofi-Pasteur, Paladin, Roche Molecular Systems, and Valeant. Ms. Stutz and Dr. Rampakakis report personal fees from Merck Canada and are employees of JSS Medical Research.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jogc.2018.05.024.

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