

# Human Papillomavirus (HPV) Vaccine

Technical Report  
July 2017

## Public Health Ontario

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# Introduction

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Since the 2007-08 school year, Ontario has had a publicly-funded, school-based human papillomavirus (HPV) vaccination program for girls using the quadrivalent vaccine, Gardasil®<sup>1</sup> or HPV4. The Ontario program is locally administered by the 36 public health units (PHUs). Initially the program was offered to Grade 8 female students who are approximately 13 years of age and using a 3-dose series. In keeping with previous Provincial Infectious Diseases Advisory Committee on Immunization (PIDAC-I) recommendations,<sup>2</sup> beginning in the 2015-16 school year, the number of doses in the series was reduced to two. In the 2016-17 school year, several additional changes were made to the program. Both boys and girls became eligible to receive HPV4 vaccine and the program was moved to offer vaccination in Grade 7, rather than Grade 8.<sup>3</sup> For the 2016-17 school year only, girls in both grades were vaccinated, in order to ensure that Grade 8 girls would not miss the opportunity to be vaccinated. Students remain eligible to receive the HPV vaccine series until the end of their Grade 12 year.

There are currently three HPV vaccines available in Canada. Gardasil® was authorized for use in Canada in 2006<sup>4</sup> and was approved as a 2-dose schedule for persons aged 9 to 13 years in March 2015. The bivalent vaccine (HPV2), Cervarix™,<sup>5</sup> was authorized for use in Canada in 2010<sup>6</sup> and was approved as a 2-dose schedule for persons aged 9 to 14 years in July 2014. HPV4 vaccine protects against HPV types 6, 11, 16, 18 and HPV2 protects against types 16 and 18. In February 2015, a nonavalent vaccine (HPV9), Gardasil®9,<sup>7</sup> was authorized for use in Canada.<sup>8</sup> HPV9 protects against five additional HPV types (HPV 31, 33, 45, 52, and 58). In December 2016, HPV9 was approved as a 2-dose schedule for persons aged 9 to 14 years.<sup>7</sup>

There have been five National Advisory Committee on Immunization (NACI) statements pertaining to HPV vaccines published between 2007 and 2016,<sup>9-13</sup> one of which is not yet publicly available. The fourth and fifth NACI statements provide recommendations for the use of HPV9 vaccine, the minimum intervals between doses in HPV vaccination schedules, and the use of HPV vaccines in immunocompromised individuals.<sup>12,13</sup>

## Objectives

The objectives of this report are to highlight the recommendations from the two most recent NACI statements on HPV vaccines (July and December 2016) and to provide an overview of the cost-effectiveness of different HPV vaccination strategies within the context of Ontario's routine, school-based HPV vaccination program to assist PIDAC-I in its deliberations on HPV vaccine. Duplication of details contained within the NACI updates has been avoided and the reader is referred to the NACI statements for further detailed information.<sup>12,13</sup>

# Summary of the NACI recommended Human Papillomavirus (HPV) vaccine schedule for females and males

The December 2016 NACI HPV statement contains updated recommendations on the HPV9 vaccine. The recommendations from this statement and their corresponding evidence grades are reprinted below (in bold), with supporting excerpts from the statement for each recommendation.<sup>13</sup>

## **1. Immunocompetent Females and Males 9-14 Years of Age**

***“NACI recommends that HPV9 vaccine should be offered according to either a 2-dose or 3-dose immunization schedule in immunocompetent females and males 9 to 14 years of age (as with HPV2 or HPV4 vaccines in females, and HPV4 vaccine in males in this population) – NACI Evidence Grade B Recommendation (fair evidence to recommend immunization)”***

*“There is fair evidence regarding the safety and immunogenicity of a 2-dose immunization schedule to recommend HPV9 in females and males ages 9-14, although evidence is limited in quantity. There is no evidence to suggest that individuals will respond differently to HPV9 versus HPV4 or HPV2 vaccines. For a 2-dose schedule, at least 6 months between the first and second dose is recommended.”*

## **2. Immunocompetent Females and Males ≥15 Years of Age**

***“NACI continues to recommend that HPV9 vaccine should be offered according to a 3-dose immunization schedule in immunocompetent females and males 15 years of age and older (as with HPV2 or HPV4 vaccines in females and HPV4 vaccine in males) – NACI Evidence Grade B Recommendation (fair evidence to recommend immunization)”***

*“There are currently no studies directly evaluating a 2-dose immunization schedule for HPV9 vaccine in males and females 15 years of age and older. Therefore, a 3-dose schedule continues to be recommended in these populations.”*

## **3. Immunocompromised persons as a result of disease or medications**

***“NACI continues to recommend that HPV vaccines be administered using a 3-dose schedule in immunocompromised populations according to existing age guidelines –NACI Evidence Grade B Recommendation for HPV2 and HPV4 vaccine (fair evidence to recommend immunization); NACI Evidence Grade I Recommendation for HPV9 vaccine (insufficient evidence in either quantity and/or quality to make a recommendation, however other factors may influence decision-making).”***

*“There are currently no published studies exploring a 2-dose HPV immunization schedule in immunocompromised populations. Although the immunogenicity and efficacy have not been fully characterised in all immunocompromised populations, individuals who are compromised are expected to*

*derive benefit from these vaccines and NACI continues to recommend vaccination of these groups using a 3-dose schedule to provide protection.”*

*“There are currently no studies directly evaluating the immunogenicity, efficacy, or safety of HPV9 vaccine in immunocompromised populations with either a 3-dose or 2-dose schedule. However, there is no evidence to suggest that immunocompromised populations would respond differently to HPV9 vaccine compared to either the HPV4 or HPV2 vaccines.”*

NACI also recommends that, where possible, the same HPV vaccine should be used to complete the series. If completion of the series with the same vaccine is not possible, the HPV2, HPV4 or HPV9 vaccine may be used to complete the series in females, and the HPV4 or HPV9 vaccine may be used to complete the series in males. The use of HPV9 vaccine among immunocompetent 9- to 26-year-olds is expected to provide similar protective efficacy against genotypes contained in the HPV4 vaccine.<sup>13,14</sup> The extent of protection against HPV types 31, 33, 45, 52, and 58 in a mixed series using different HPV vaccines is not clear.

The following HPV recommendations and evidence grades first appeared in the July 2016 NACI statement.<sup>12</sup> They are referenced in and remained current as of the December 2016 NACI statement:

***“NACI concludes that there is insufficient evidence at this time to recommend, at a population level, the re-immunization with HPV9 vaccine of individuals who have completed an immunization series with another HPV vaccine - NACI Recommendation Evidence Grade I.”***

***“NACI concludes that there is good evidence that the minimum interval between the first and last doses in either a 2-dose or 3-dose HPV immunization schedule should be 24 weeks (6 months) – NACI Recommendation Evidence Grade A”***

Table 1 summarizes the current NACI HPV immunization schedule recommendations and their corresponding evidence grades.

**Table 1: Summary of NACI immunization schedule recommendations as of December 2016 (reprinted from forthcoming NACI statement)<sup>13</sup>**

<b>Recommended groups</b>	<b>Recommended immunization schedule</b>	<b>Vaccines and NACI evidence grade</b>
<b>Healthy (immunocompetent, non-HIV infected) females 9-14 years of age (and healthy females ≥15 years of age in whom the first dose was administered between 9-14 years of age)</b>	2- or 3-dose schedule	HPV2 or HPV4 (Grade A) HPV9 (Grade B)
<b>Healthy (immunocompetent, non-HIV infected) females ≥15 years of age</b>	3-dose schedule	HPV2 or HPV4 (Grade A) HPV9 (Grade B)
<b>Healthy (immunocompetent, non-HIV infected) males 9-14 years of age (and healthy males ≥15 years of age in whom the first dose was administered between 9-14 years of age)</b>	2- or 3-dose schedule	HPV4 or HPV9 (Grade B)
<b>Healthy (immunocompetent, non-HIV infected) males ≥15 years of age</b>	3-dose schedule	HPV4 or HPV9 (Grade B)
<b>Immunocompromised individuals and immunocompetent HIV-infected individuals</b>	3-dose schedule	HPV2 or HPV4 in females (Grade B) HPV4 in males (Grade B) HPV9 in females or males (Grade I)

Source: Public Health Agency of Canada, National Advisory Committee on Immunization. An Advisory Committee Statement (ACS), National Advisory Committee on Immunization (NACI): Updated Recommendations on Human Papillomavirus (HPV) Vaccines: 9-valent HPV vaccine 2-dose immunization schedule and the use of HPV vaccines in immunocompromised populations [forthcoming]. Ottawa, ON: Her Majesty the Queen in Right of Canada; [2017]. Used with permission.

# Economic Considerations

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As of December 2016, NACI did not include economic or other programmatic considerations while formulating their vaccine recommendations. The following section briefly outlines the anticipated cost-effectiveness of Ontario's routine, school-based HPV vaccination program using various HPV vaccine strategies.

## Review of cost effectiveness of HPV9 versus HPV4 vaccine

Cost-effectiveness is a key consideration for vaccination program decision-making in Canada.<sup>15</sup> There is emerging evidence regarding the cost-effectiveness of the HPV9 vaccine in various settings.<sup>16-20</sup> Drolet et al. examined the cost of vaccinating girls with three doses of the HPV9 vaccine compared to 3-doses of the HPV4 vaccine in Canada.<sup>16</sup> The authors used an individual-based transmission-dynamic mathematical model of HPV infection and disease titled Agent-based Dynamic Model for Vaccination and Screening Evaluation (HPV-ADVISE) and applied a health care payer perspective, 70-year time horizon, and 3% annual discount rate for costs and benefits. The model was calibrated to account for Canadian sexual behaviour, screening, and epidemiologic data. Various HPV-related diseases were modeled including cancers (cervical, vaginal, vulvar, anal, penile, oropharyngeal) and anogenital warts (AGWs). The model was run numerous times and the results represent the median of the varying simulation outputs. The tenth and ninetieth percentiles of pooled model outputs are also provided in parentheses. The base-case assumptions were vaccination of 10-year old girls; 95% vaccine efficacy; 80% coverage; 20-year vaccine duration; 10-year quadrivalent cross protection against HPV-31/33/45/52/58 with 46%/29%/8%/18%/6% efficacy, respectively; and a cost of \$95/dose for both HPV4 and HPV9 vaccines. Sensitivity analyses were conducted by varying the following model parameters: duration of vaccine protection (lifelong), vaccine coverage (50% and 70%), proportions of disease burdens of cancers and AGWs, HPV9 vaccine efficacy (90% and 85%), and disease outcomes (cervical cancer only; cervical cancer and AGWs).

The results indicate that under base-case assumptions, using HPV9 vaccine is estimated to cost \$12,203 [9,331; 17,292], per quality-adjusted life year (QALY) gained, whereas using HPV4 vaccine is estimated to cost \$15,528 [12,056; 19,140] per QALY gained. When varying parameters in sensitivity analyses, both vaccines remained below a \$40,000/QALY gained threshold. The authors also determined that the additional cost per dose of the HPV9 vaccine should not exceed \$11 [4; 17] for it to remain more cost-effective than the HPV4 vaccine and should not exceed an additional \$24 [6; 36] per dose to be a cost-effective intervention using a \$40,000/QALY gained threshold. In sensitivity analyses, the additional cost per dose for HPV9 vaccine to be as cost-effective as HPV4 vaccine ranges between \$4 and \$18; and the additional cost per dose for HPV9 vaccine to remain cost-effective using a \$40,000/QALY gained threshold ranges between \$8 and \$37. The authors did not examine the cost-effectiveness of HPV vaccination of boys or gender-neutral HPV vaccination.

In January 2017 PIDAC-I considered an evaluation comparing the cost-effectiveness of switching to the use of the HPV9 vaccine from the HPV4 vaccine in Ontario using HPV-ADVISE.<sup>21</sup> As Ontario currently has a gender-neutral 2-dose HPV4 program delivered in Grade 7, this was considered the base-case and only scenarios applicable to this base-case were considered. Therefore, scenarios focusing on female-only programs and using a 3-dose rather than a 2-dose series were deemed not applicable. The analysis used a health care payer perspective with a 100-year time horizon and 3% discount rate. The model was calibrated to account for Canadian sexual behaviour, screening, and epidemiologic data. The model was run numerous times and the results represent the median of the varying simulation outputs. The 10<sup>th</sup> and 90<sup>th</sup> percentiles of pooled model outputs are also provided in parentheses. The base-case assumptions were vaccination of 11-year old children, 95% vaccine efficacy; 80% coverage; lifelong vaccine duration; lifelong quadrivalent cross protection against HPV-31/33/45/52/58 at 46%/29%/8%/18%/6% efficacy, respectively; and a vaccine cost of \$92/dose for HPV4 and \$100/dose for HPV9 (i.e., \$8 price differential). Sensitivity analyses were conducted by varying the following model parameters: duration of vaccine protection (10 years; 20 years; 30 years), vaccine coverage (50%; 65%; 85%); age at vaccination (10 years; 14 years), and assuming no quadrivalent cross-protection for the five additional genotypes.

The results suggest that under base-case assumptions, switching to a 2-dose HPV9 vaccination program from an HPV4 program for both girls and boys is likely to be cost-effective. These findings were robust across a wide range of plausible assumptions, such as duration of protection, cross-protection or no cross-protection, age at vaccination, and vaccine coverage. Switching from a gender-neutral HPV4 program to a gender-neutral HPV9 program would cost \$3,700 per QALY gained [cost saving; 16,500] with sensitivity analyses indicating a cost range of \$60 to \$19,600 per QALY gained. It was noted that changing the base cost per dose for each vaccine would not affect the results, provided that the absolute difference in cost between the vaccines remains the same.

The cost-effectiveness of an HPV9 vaccination program versus an HPV4 vaccination program is largely derived from the protection conferred to females against the five additional HPV genotypes, as the burden of illness associated with the five additional genotypes is not equally shared between the sexes. Under base-case assumptions, switching to HPV9 vaccination from HPV4 vaccination is expected to reduce high-grade precancerous cervical lesions (CIN2/3) by 14% to 27% and reduce cervical cancer by 9% to 20% (ranges obtained by varying key assumptions of vaccine duration and cross-protection) and subsequently reduce costs associated with treating these illnesses. While HPV9 vaccination offers protection against HPV-related cancers that affect males, the population burden of disease of these cancers is comparatively lower than CIN2/3 and cervical cancer.<sup>10</sup> Accordingly, the results suggest that switching girls only to 2-dose HPV9 vaccination while maintaining 2-dose HPV4 vaccination for boys is likely to be cost saving [cost saving; 4,900].<sup>19</sup> However, offering different vaccine products to girls and boys in a school-based program presents logistical challenges and ethical concerns.

These findings were similar to studies examining the cost-effectiveness of HPV9 versus HPV4 vaccine in the United States, Austria, and Australia.<sup>17,19,20</sup> In these settings, switching to an HPV9 vaccination program from an HPV4 program was found to be cost-effective. The US study suggested that switching

to HPV9 vaccination of girls only (and maintaining HPV4 vaccination of boys) was more cost-effective compared to gender-neutral HPV9 vaccination.<sup>19</sup>

While cost-effectiveness studies are crucial for decision-making, they are not without limitations which include some uncertainty regarding key model parameters such as duration of HPV vaccine protection and cross-protection. In addition, many studies include oral pharyngeal cancers in the model, whereas HPV vaccine is not currently licensed to prevent this outcome. HPV9 may have more favourable cost-effectiveness results if a societal perspective was taken rather than a health care payer perspective.

## Other Considerations

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The anticipated cost-effectiveness of HPV9 vaccination should be interpreted along with other factors including operational, programmatic, logistical, acceptability, and ethical/equity considerations when determining whether HPV4 or HPV9 vaccine should be used in the routine, school-based HPV vaccination program in Ontario.

There are no operational or programmatic concerns with changing from HPV4 to HPV9 vaccine. Both products are supplied by the same manufacturer and are administered in the same way. Therefore, as long as the same vaccine is used for both sexes, transition from one product to the other should be relatively seamless. Providing two different HPV vaccines to the different sexes would present logistical and communication difficulties for the PHUs administering the school-based program, including the potential for error in delivery, the development and distribution of different consent forms, and distinct communication materials for parents/guardians including the rationale for different vaccines for male and female students. In addition, there are ethical considerations if male students received an HPV vaccine which offers less protection than the vaccine offered to female students.

Regarding vaccine acceptability, there is no evidence to suggest that eligible recipients of HPV vaccine or their parents/guardians would consider HPV9 vaccine less acceptable than HPV4 vaccine. In fact, continuation of a program using HPV4 vaccine may be associated with less public and provider acceptance, given the availability of another vaccine that offers protection to a larger number of HPV genotypes. In addition, the continued use of HPV4 vaccine may prompt parents/guardians with the ability to pay to withdraw their children from the school-based program in favour of paying for HPV9 vaccine. This has ethical and equity implications, as the degree of protection against HPV-related disease could be associated with ability to pay. HPV9 vaccine provides protection against five additional genotypes compared to HPV4 vaccine. These genotypes are associated with approximately 15-19% of cervical cancers, up to 30% of high-risk precancerous cervical lesions, and 14% of anogenital cancers.<sup>12</sup> Communication materials would need to be updated to reflect the enhanced protection of HPV9 versus HPV4 vaccines (i.e., five additional genotypes). Providing HPV9 vaccine, as opposed to HPV4 vaccine, to students in the publicly-funded program would allow for equitable access to maximal protection against risks associated with HPV, as vaccine receipt would not be associated with ability to pay.

## Conclusion

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This report was developed in order to assist PIDAC-I in providing advice on HPV vaccines in the context of Ontario's publicly-funded, school-based HPV vaccination program. It summarizes the two most recent NACI recommendations on HPV vaccines including updated HPV9 recommendations prepared in December 2016. This report also summarizes information on the anticipated cost-effectiveness of a routine adolescent program using HPV9 vaccine, as compared to the HPV4 vaccine. The determination of which vaccine should be used in Ontario's HPV vaccination program should consider the most recent evidence on HPV vaccines and findings from cost-effectiveness assessments, as well as programmatic, operational, logistical, acceptability, and ethical/equity considerations.

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