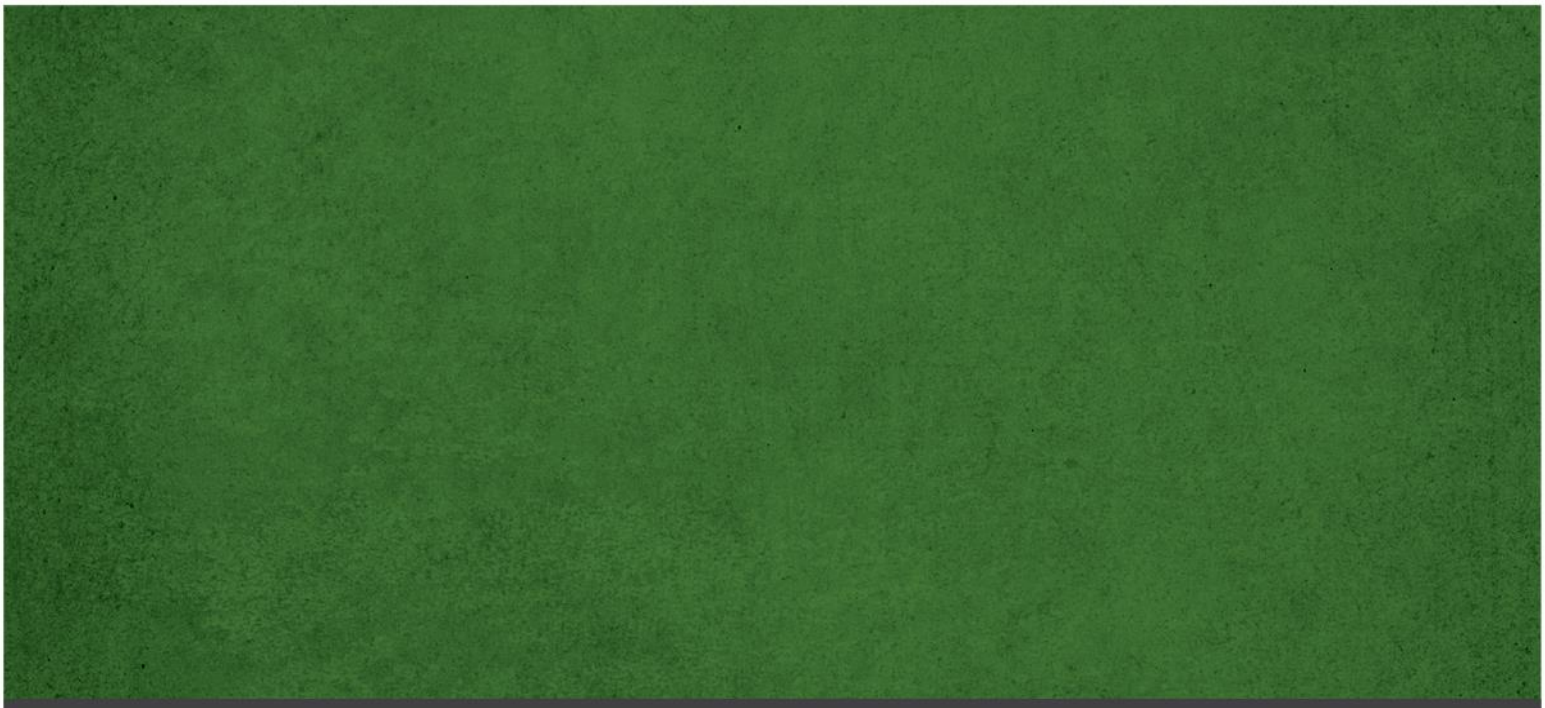
An Advisory Committee Statement (ACS)

National Advisory Committee on Immunization (NACI)

Updated Recommendations on Human Papillomavirus (HPV) Vaccines



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To obtain additional information, please contact:

Public Health Agency of Canada
Address Locator 0900C2
Ottawa, ON K1A 0K9
Tel.: 613-957-2991
Toll free: 1-866-225-0709
Fax: 613-941-5366
TTY: 1-800-465-7735

E-mail: publications-publications@hc-sc.gc.ca

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PREAMBLE

The National Advisory Committee on Immunization (NACI) is an External Advisory Body that provides the Public Health Agency of Canada (PHAC) with independent, ongoing and timely medical, scientific, and public health advice in response to questions from PHAC relating to immunization.

In addition to burden of disease and vaccine characteristics, PHAC has expanded the mandate of NACI to include the systematic consideration of programmatic factors in developing evidence-based recommendations to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels.

The additional factors to be systematically considered by NACI include: economics, ethics, equity, feasibility, and acceptability. Not all NACI statements will require in-depth analyses of all programmatic factors. While systematic consideration of programmatic factors will be conducted using evidence-informed tools to identify distinct issues that could impact decision-making for recommendation development, only distinct issues identified as being specific to the vaccine or vaccine-preventable disease will be included.

This statement contains NACI's independent advice and recommendations, which are based upon the best current available scientific knowledge. This document is being disseminated for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph. Recommendations for use and other information set out herein may differ from that set out in the product monographs of the Canadian manufacturers of the vaccines. Manufacturer(s) have sought approval of the vaccines and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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I. INTRODUCTION

Globally and in Canada, HPV-associated diseases are a significant public health problem. Human papillomavirus (HPV) infection is very common in Canada. Without vaccination, it is estimated that 75% of people will have at least one HPV infection in their lifetime. HPV-associated diseases include anogenital cancers such as cervical cancer and anal cancer, as well as oropharyngeal cancer.

HPV vaccination, along with surveillance and screening strategies, are core public health measures for the prevention of HPV-associated cancers. The current goal of the Canadian HPV Immunization program is to reduce vaccine preventable HPV-related morbidity and mortality in the Canadian population [(1)]. Additionally, the Canadian Strategy for Cancer Control calls for the elimination of cancers caused by HPV through universal access to HPV vaccine programs for all children, delivered in a culturally sensitive way [(2)]. As part of Canada's commitment to the country's action plan, which aligns with the World Health Organization's (WHO) cervical cancer elimination initiative, Canada has set a national target to achieve 90% vaccination coverage for two or more doses of HPV vaccines by 17 years of age [(3)]. The goal aligns with HPV vaccination goals set forth in the Canadian Partnership Against Cancer Action Plan for the Elimination of Cervical Cancer in Canada [(4)].

Rates for completion of a 2-dose HPV vaccine series in the context of school-based immunization programs continue to vary across Canadian provinces and territories. The most recent publication from the Canadian Partnership Against Cancer Action reports HPV vaccination rates varying between 57 to 91%, based on data from the 2017/2018 school year [(4)]. A more recent report from the Canadian Childhood National Immunization Survey from 2021 indicates approximately 84% of 14-year-olds received 1 or more HPV vaccine dose. While this is an increase from 80% vaccine coverage rates in 2019, HPV vaccine coverage rates continue to fall short of the national goal [(5)].

NACI last issued an updated recommendation on HPV vaccine schedules in 2017, recommending a 2- or 3-dose schedule for those aged 9 to less than 15 years and a 3-dose schedule for older individuals (e.g., 15 years of age and older) as well as those considered immunocompromised or living with HIV. The 2017 guidance considered available evidence at the time, as well as changes to the authorized usage of HPV vaccine allowing for a 2-dose series.

Since then, numerous trials and studies have reported on the benefit of a 1-dose schedule. In December 2022, the WHO issued updated guidance on HPV vaccine schedules noting a single-dose schedule, referred to as an alternative, off-label single–dose schedule, can provide a comparable efficacy and durability of protection to a 2-dose regimen for individuals aged 9 to 20 years. The WHO now recommends:

- A 1- or 2-dose schedule for girls aged 9 to 14 years
- A 1- or 2- dose schedule for girls and women aged 15 to 20 years

- 2 doses with a 6-month interval for women 21 years of age and older [6]

The WHO also notes that the primary target of vaccination is girls aged 9 to 14 to prevent cervical cancer, however secondary populations such as boys and older females are recommended where feasible and affordable [6].

Given ongoing efforts to improve HPV vaccination coverage and reduce HPV-associated burden of disease among people in Canada, and considering recent updated guidance from the WHO, Canadian provinces and territories requested that NACI update guidance on HPV vaccine schedules. NACI also considered additional program updates including updates to the authorized indication of 9vHPV (nonavalent HPV vaccine Gardasil-9, Merck; expanded authorization now includes males 27 to 45 years of age). Updated NACI guidance on the use of HPV vaccines was discussed at NACI on February 8 and April 17, 2024 and approved on May 27, 2024.

Guidance Objective:

The objective of this advisory committee statement is to review evidence and provide guidance on the recommended use of HPV vaccines, including updated guidance on populations recommended to receive HPV vaccines and updated recommendations on HPV vaccine schedules.

II. METHODS

In brief, the broad stages in the preparation of this NACI statement were:

1. Analysis of the burden of HPV-associated diseases in Canada and worldwide.
2. Knowledge synthesis: retrieval and summary of individual studies and existing systematic reviews, assessment of the certainty of the evidence from individual studies – summarized in Montroy et al., 2024.
3. Synthesis of the body of evidence of benefits and harms, considering the quality of the synthesized evidence and magnitude of effects observed across the studies outlined above.
4. Mathematical modelling on HPV disease projections if Canadian provinces and territories switch to a 1-dose policy [7].
5. Use of a published, peer-reviewed framework and evidence-informed tools to ensure that issues related to ethics, equity, feasibility, and acceptability (EEFA) are systematically assessed and integrated into the guidance [8].
6. Economic evaluation: While an economic evaluation of the impact of a 1-dose HPV immunization program in Canada was not conducted, NACI reviewed 3 published economic evaluations comparing 1- versus 2-dose HPV vaccination schedules in high-income settings.
7. The evidence and programmatic considerations were organized using a GRADE-informed

process and all of the information was used to facilitate NACI guidance development.

Further information on NACI's evidence-based methods can be found online [9].

For this advisory committee statement, NACI reviewed the key questions as proposed by the HPV Working Group, including such considerations as the disease burden of HPV-associated illnesses, surveillance for HPV infections and associated diseases, the safety, immunogenicity, efficacy, effectiveness of HPV vaccines currently marketed in Canada by schedule (e.g., number of doses administered), the safety of HPV vaccination during pregnancy, and other aspects of the overall immunization strategy. The knowledge synthesis was performed by the NACI secretariat and supervised by the HPV Working Group. Following critical appraisal of individual studies, summary tables with ratings of the certainty of the evidence using GRADE methodology were prepared (Montroy et al., 2024.

NACI consulted the Public Health Ethics Consultative Group (PHECG) about ethical considerations related to a 1-dose HPV vaccine policy switch for Canada as well as the Canadian Immunization Committee for feedback from Canadian jurisdictions on the feasibility of alternative HPV vaccine schedules.

Mathematical modelling was used to project the potential population-level impact of switching from a 2- to 1-dose routine HPV vaccination program in Canada, using different assumptions of vaccine efficacy (VE) and duration of vaccine (VD) protection [7].

The Working Group chair and PHAC NACI secretariat presented the evidence and proposed recommendations to NACI on February 8, 2024. Following thorough review of the evidence and consultation at the NACI meetings of February 8, 2024, and April 17, 2024, recommendations on HPV programs were approved by NACI on (x date). The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the text. The full knowledge synthesis of clinical evidence on 1-dose HPV schedules can be found here: Montroy et al., 2024.

III. EPIDEMIOLOGY

III.1 HPV virus types and associated diseases

Human papillomaviruses (HPV) are small, double-stranded DNA viruses that infect the epithelium. Most HPV infections occur without any symptoms and resolve without treatment. Over 200 HPV genotypes have been identified, including approximately 40 that preferentially infect anogenital and oropharyngeal sites. Persistent infection with high-risk types (e.g., HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) can result in cervical, oropharyngeal, vaginal, vulvar, penile, and anal cancers. Low-risk types (e.g., HPV6 and 11) are generally non-oncogenic but cause conditions such as anogenital warts (AGW) and recurrent respiratory papillomatosis

(RRP). Data is also suggestive of a possible association between HPV infections during pregnancy and adverse outcomes to both the pregnant woman or pregnant individual and the fetus [10-12].

III.2 Burden of disease in Canada

Without vaccination, it is estimated that 75% of people in Canada will have at least one HPV infection in their lifetime [13]. The highest prevalence is in young adults aged 20 to 24 [14]. HPV is responsible for almost 3,800 new cancer cases annually in Canada [15]. HPV-associated cancer risk varies by anatomical region and age. Notably, oropharyngeal, vaginal, vulvar, penile, and anal cancers are more likely to occur at older ages compared to cervical cancer [16].

Cervical cancer
In Canada, HPV is responsible for virtually all cervical cancers, with over 70% due to HPV16 and HPV18 alone and 90% due to all high-risk HPV types targeted by the 9vHPV vaccine [16-20]. Approximately 1,550 new cases of cervical cancer and 400 deaths were estimated for Canada for 2023 [21]. It is the 14th most common cancer among females and the 4th most common among those aged 15 to 44 years in Canada [16].

Other HPV-associated cancers
Nearly two-thirds of HPV-associated cancers are non-cervical and approximately one-third of HPV-associated cancers are in males [13]. Specifically, HPV causes 90% of anal cancers, 40% of vaginal and vulvar cancers, 40 to 50% of penile cancers, and 60 to 73% of oropharyngeal cancers, making oropharyngeal cancer the most frequent HPV-associated cancer in Canada [13, 22, 23].

Oropharyngeal cancer
There has been a steady increase in the proportion of oropharyngeal cancers attributed to HPV infections in Canada in recent decades, consistent with data from the United States [22, 24-26]. HPV-associated oropharyngeal cancers show a significantly better survival rate compared to non-HPV oropharyngeal cancers [25-27]. Oropharyngeal cancers caused by HPV are known to have a long latency period between the infection and the onset of cancer [28]. There is no established screening method to detect early disease [29-31].

Peak age for HPV-associated cancers
Peak incidence of HPV-associated cancers varies by cancer type. Cervical cancer peaks in incidence at age 40 to 44 [16]. Vaginal, vulvar, and penile cancers tend to peak at age 85 and older [16]. Among Canadian males and females, the onset of anal and oropharyngeal cancers is typically between 60 to 70 years of age [16].

Other HPV-associated diseases

AGW is one of the most common sexually transmitted infections worldwide, with HPV6 and HPV11 accounting for up to 90% of AGW cases [13, 32]. Higher rates of AGW are consistently observed among males compared to females, peaking at 25 to 29 years for males and 20 to 24 years for females [33-35]. Available evidence on annual incidence of AGW is limited to a 2017 study, estimating rates between 113.3 to 154.0 per 100,000 males and 94.6 to 121.0 per 100,000 females [34]. Data from 2000-2017 in British Columbia showed an overall decline of 56% in AGW rates among both sexes following the introduction of the provincial school-based HPV immunization program [35]. Juvenile onset RRP (JoRRP) is acquired by vertical transmission of HPV6 or HPV11. While severe, it is very rare, with an annual incidence of 0.24 cases per 100,000 children 14 years of age and younger [36]. While there is no data specific to Canada, evidence from other jurisdictions indicates that the incidence of JoRRP has been decreasing since the introduction of routine HPV immunization programs [37, 38]. Data pertaining to the incidence of adult onset RRP is currently limited. Overall, the burden of AGW and RRP are not well studied in Canada and updated surveillance is needed to better understand the prevalence of these diseases.

Risk of HPV infection in pregnancy

Pregnant women and pregnant individuals are at risk of HPV infection. Results of epidemiological studies suggest that maternal HPV infection might increase the risk of pregnancy complications, such as spontaneous abortion, preterm birth, preeclampsia, intrauterine growth restriction, premature rupture of membranes, and fetal death [11, 39].

III.3 Summary of HPV immunization programs in Canada

School-based programs

HPV vaccination is currently offered to school-aged children and adolescents across Canadian provinces and territories as part of publicly funded school-based programs. These programs initially launched in 2007/2008 for female students and were expanded to both biological sexes by 2017 in all provinces and territories [15]. Most jurisdictions exclusively use the 9vHPV vaccine, except Quebec, which uses the 2vHPV vaccine (Bivalent vaccine; Cervarix, GSK) as a second dose in their mixed schedule [40].

Other programs

In addition to school-based HPV immunization programs, publicly funded catch-up programs are available to select populations across provinces and territories, with varying eligibility by age and other factors. The vaccine is available for private purchase for those who are not included in their jurisdiction's publicly funded HPV immunization programs [15, 41].

III.5 Populations with reduced vaccine coverage

Increasing HPV vaccination coverage to reduce the prevalence of HPV-associated diseases remains a public health priority in Canada [2]. In 2021, it was estimated that 84% of 14-year-old adolescents across Canada received at least one dose of the HPV vaccine [5].

More recent national data (since 2021) is not available; however vaccine coverage data up to 2023 is available for select provinces and territories. As of April 29, 2024, 5 provinces and 1 territory (Alberta, Saskatchewan, Manitoba, New Brunswick, Nova Scotia and Yukon) submitted reports to PHAC as part of the Standardized Reporting on Vaccination (STARVAX) initiative. Additional provinces and territories are anticipated to participate in future reporting.

Table 1. HPV vaccination coverage for 14-year-olds in 6 provinces and territories (AB, SK, MB, NB, NS, and YT) combined, 2019 to 2023.[1]

	2019		2020		2021		2022		2023	
Dose	**≥1**	**2**	**≥1**	**2**	**≥1**	**2**	**≥1**	**2**	**≥1**	**2**
Females	80.6%	75.0%	80.0%	75.1%	81.8%	75.2%	80.7%	70.3%	77.1%	67.9%
Males	67.4%	62.2%	78.5%	73.4%	79.6%	72.2%	78.5%	68.0%	75.0%	65.7%
All children	73.8%	68.4%	79.3%	74.3%	80.7%	73.7%	79.6%	69.1%	76.1%	66.8%

[1]Source: Standardized Reporting on Vaccination (STARVAX)
Coverage estimates as of December 31 of each year, respectively. Coverage is calculated based on aggregate data provided from Canadian jurisdictions on the number of children vaccinated, using population size estimates as denominators.

Among participating provinces and territories, 76.1% of adolescents 14 years of age received at least one dose of HPV vaccine, and 66.8% received two doses in 2023 (Table 1). Vaccine uptake (at least one dose) in 2023 was slightly higher among females (77.1%) than males (75%), and this difference was consistent with data from previous years [5]. There is also regional variability in HPV vaccine coverage in Canada. Data from Canadian school-based HPV vaccine programs spanning 2015 to 2018 estimates coverage ranging from 57 to 91% across Canadian provinces and territories [42]. Recent data used to inform Canadian-specific 1-dose HPV program disease modelling also highlights this regional variability, with coverage with two doses of vaccine substantially higher among Québec adolescents compared to Ontario adolescents [7].

As Canadian provinces and territories do not routinely report on vaccine coverage disaggregated by race or ethnicity, data regarding HPV vaccine coverage among equity-denied groups is currently limited. Available evidence suggests that HPV vaccination is lower among First Nations, Métis, and Inuit populations in Canada [43].
Overall, the available data highlights that in addition to a need to increase immunization in order to meet current goals, there is need for more detailed vaccine coverage reporting across and within Canadian jurisdictions, as well as within subpopulations with existing health inequities. Additionally, since 2020, the COVID-19 pandemic has disrupted school-based immunization programs and substantially reduced HPV vaccine uptake across the country [44-46]. Recent studies indicate that coverage has yet to return to pre-pandemic levels [45, 46].

IV. VACCINE

IV.1 Preparation(s) authorized for use in Canada

Characteristics of the HPV vaccines currently available in Canada are summarized below.

Table 2. Comparison of HPV vaccines currently available in Canada[1]

	9vHPV	2vHPV
Manufacturer	Merck Canada Inc.	GlaxoSmithKline Inc.
Date of authorization in Canada	2015	2010
Type of vaccine	Protein subunit	Protein subunit
HPV types[2]	6, 11, 16, 18, 31, 33, 45, 52, 58	16, 18
Adjuvant	Amorphous aluminum hydroxyphosphate sulfate (AAHS)	AS04
Formats available	Single-dose pre-filled syringe	Single-dose pre-filled syringe
Route of administration	Intramuscular	Intramuscular
Authorized indications	Individuals aged 9 to 45 years	Females aged 9 to 45 years
Contraindications	Persons with a history of anaphylaxis after previous administration of the vaccine and in persons with proven immediate or anaphylactic hypersensitivity to any component of the vaccine or its container	Persons with a history of anaphylaxis after previous administration of the vaccine and in persons with proven immediate or anaphylactic hypersensitivity to any component of the vaccine or its container
Precautions	Not recommended for use in pregnancy	Not recommended for use in pregnancy

Storage Requirements	Should be stored at +2°C to +8°C, should not be frozen, and should be protected from light.	Should be stored at +2°C to +8°C, should not be frozen, and should be protected from light.

[1]Gardasil quadrivalent HPV vaccine (4vHPV) was authorized in 2006 in Canada and discontinued in 2019.
[2] Refer to Contents of immunizing agents authorized for use in Canada in Part 1 of the Canadian Immunization Guide (CIG) for a complete list of ingredients.

For complete prescribing information for 9vHPV and 2vHPV vaccines, consult the product leaflet or information contained within Health Canada's authorized product monographs available through the Drug Product Database.

IV.2 Clinical evidence on HPV vaccine schedules by dose number

NACI reviewed available evidence on the efficacy, effectiveness and immunogenicity of reduced dose HPV vaccination schedules. The majority of available evidence to date demonstrates the efficacy, effectiveness and immunogenicity of reduced dose schedules in young, healthy females (i.e., 20 years of age and younger). Data on reduced dose schedules in older age groups and in males is currently limited. Additional clinical trials on 1-dose HPV vaccine schedules in expanded populations are expected in the coming years. A summary of the key evidence used to inform decision-making is outlined below. Please see Montroy et al, 2024 Mfor further detail on individual studies, including a certainty of evidence assessment using GRADE methodology.

Efficacy and effectiveness

IV.2.1 Efficacy and Effectiveness of a 1-dose HPV vaccine schedule compared to no HPV vaccine

Compared to no HPV vaccine, the available evidence from randomized controlled trials (RCTs) demonstrated that a 1-dose HPV vaccine schedule resulted in a large reduction in persistent HPV infections with product-specific vaccine types, through 3 years following vaccination (high certainty of evidence) [(47)]. Evidence from non-randomized trials demonstrated similar effects, with a single dose of HPV vaccine resulting in reductions of persistent, incident and prevalent HPV infections with product-specific vaccine types, compared to no vaccine (moderate certainty of evidence; follow-up ranging from 6 to 11 years) [(48-51)], as well as reductions in AGW (moderate certainty of evidence; follow-up of approximately 2.5 years) [(52)].

IV.2.2 Efficacy and effectiveness of a 1-dose HPV vaccine schedule compared to a 2- or 3-dose HPV vaccine schedule

Compared to a 2- or 3-dose schedule, available evidence suggests that a 1-dose schedule may provide similar protection from HPV infection with product-specific vaccine types, through 11 years following vaccination. Compared to 2 or 3 doses, there may be little to no difference in the risk of persistent, incident or prevalent HPV infections with product-specific vaccine types (low certainty of evidence, follow-up ranging from 4 to 11 years) [48-50], or in the risk of AGW (low certainty of evidence; follow-up of approximately 2.5 years), with a 1-dose HPV vaccine schedule [52]. Similarly, there may be little to no difference in the risks of cervical abnormalities or cervical intraepithelial neoplasia grade 2+ (CIN2+) between one and either 2- or 3-dose schedules (low certainty of evidence; follow-up of 10 years), although evidence is currently limited [49].

IV.3 Immunogenicity

Numerous clinical trials have demonstrated a 1-, 2-, or 3-dose HPV vaccine series generates a robust immunological response to HPV vaccine antigens. While a 2- or 3-dose schedule results in significantly higher antibody titers compared to a 1-dose schedule, the response generated by a 1-, 2-, or 3-dose HPV vaccine schedule first peaks then remains relatively stable out to 16 years. Compared to natural infection, a single dose results in significantly higher antibody titres, out to at least 10 years [53, 54]. Currently, there is no established correlate of protection for HPV, and therefore the clinical relevance of differences in the immune response following different HPV vaccine schedules is unknown.

IV.3.1 HPV16/18 antibody titers following a 1-dose HPV vaccine schedule compared to no vaccine/placebo/control

Current evidence suggests that a single dose of HPV vaccine results in higher antibody titres compared to no vaccine (high certainty of evidence; follow-up ranging from 4 to 10 years) [51, 53, 54].

IV.3.2 HPV16/18 antibody titers following a 1-dose HPV vaccine schedule compared to a 2- or 3-dose HPV vaccine schedule

When compared to 2 or 3 doses of HPV vaccine, a 1-dose schedule of HPV vaccine results in lower antibody titers (high certainty of evidence; follow-up ranging from 2 to 16 years) [54-56]. However, the level of antibody titers induced by a single dose is several-fold higher than those generally observed after natural infection, and appears to be stable over time, through 16 years following vaccination. Several RCTs have demonstrated that the antibody titers produced by a 2-dose schedule are generally non-inferior to those produced by a 3-dose schedule [55, 57-60].

IV.4 Vaccine safety

IV.4.1 Adverse events following immunization with 9vHPV

According to 9vHPV clinical trial data, the most common injection-site reactions following vaccination in those 9 to 26 years of age were pain, swelling, and redness. The most common systemic reactions included headache and fever (37.8°C or greater) for both sexes, as well as nausea for females. Female participants reported higher frequency of adverse events (AEs) following the third dose of 9vHPV compared to the first two doses for all outcomes except any pain, which was highest following the second dose in females aged 16 to 26 years [(61)]. For males, injection site AEs were generally similar after the first, second, and third doses; however, the frequency of vaccine-related systemic events was highest following the first dose and decreased following subsequent doses [(62)].

IV.4.2 Adverse events following immunization with 2vHPV

According to 2vHPV clinical trial data, the most common injection-site reactions following vaccination were pain, swelling, and redness, while the most common systemic reactions included fatigue, headache, and myalgia in female participants aged 10 to 25 years. These participants reported higher frequency of AEs following the third dose of 2vHPV compared to the first two doses for all outcomes except any pain, which was highest following the first dose. Data on AEs by dose number is limited to studies with female participants [(63)].

IV.4.3 Post-market safety surveillance reporting data on HPV vaccines in Canada

Following release of the updated NACI recommendations on 2-dose 9vHPV vaccine in 2017, the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) received a total of 1,003 reports of AEs related to HPV vaccines administered between January 1, 2018, and September 14, 2023. Of the reports with a specified vaccine type, there were 906 reports following receipt of 9vHPV, 65 reports following 4vHPV, and 23 reports following bivalent HPV vaccine 2vHPV. Where dose number was reported, the majority (66%) followed dose 1 and 29% followed dose 2. Injection site reactions were the most frequently reported event. Forty-eight of the total 996 reports were serious, including 22 allergic reactions and 5 local reactions. No safety signals of concern were identified.

IV.4.4 Safety of HPV vaccination during pregnancy

In a 2018 systematic review from the Cochrane Collaboration, the safety of HPV vaccination during pregnancy was evaluated in those who became pregnant while participating in HPV vaccine trials (compared to placebo or a non-HPV vaccine) [(64)]. Among those who became pregnant during

the trials, there was no increased risk of miscarriage or pregnancy termination (high certainty of evidence) associated with HPV vaccination. There was also no increased risk observed for stillbirths or congenital malformations associated with HPV vaccination during pregnancy (moderate certainty of evidence), although analyses lacked sufficient power to rule out small increases or decreases in risk due to low overall event rates in the population.

The findings from a recent systematic review with a similar objective was consistent with the review from the Cochrane Collaboration, reporting no increased risk of adverse pregnancy outcomes being associated with HPV vaccination during or around pregnancy [65]. There is however, limited statistical power to detect differences in outcomes which occur with rarity (i.e., stillbirths).

Evidence specific to the safety of 9vHPV vaccination during or around pregnancy is currently limited to 2 studies. Available data indicates no increased risk of adverse pregnancy outcomes associated with 9vHPV during or around pregnancy, and any adverse outcomes appear to occur at similar rates as observed in the general population.

A theoretical risk of adverse pregnancy outcome associated with HPV vaccination during pregnancy should be balanced against the risk associated with HPV infection during pregnancy. See section III.2 for more details.

IV.5 Concurrent administration with other vaccines

HPV vaccine may be administered concurrently with other age-appropriate vaccines at different injection sites, using separate needles and syringes. HPV vaccine should be administered after other vaccines because it is known to cause more injection pain. Refer to Timing of Vaccine Administration in Part 1 of the CIG for additional information about concurrent administration of vaccines.

IV.6 Contraindications and precautions

HPV vaccine is contraindicated in persons with a history of anaphylaxis after previous administration of the vaccine and in persons with proven immediate or anaphylactic hypersensitivity to any component of the vaccine or its container. Individuals who develop symptoms indicative of hypersensitivity after receiving a dose of HPV vaccine should not receive further doses.

Refer to Contents of immunizing agents authorized for use in Canada in Part 1 of the Canadian Immunization Guide for a list of vaccines authorized for use in Canada and their contents and Contraindications and Precautions in Part 2 of the CIG for additional information.

V. DISEASE MODELLING

Mathematical modelling was used to project the potential population-level impact of switching from a 2- to 1-dose routine HPV vaccination program in Canada, using different assumptions of vaccine efficacy (VE) and duration of vaccine (VD) protection [7]. Model projections were generated using the HPV-ADVISE model, which has been extensively peer reviewed and validated and has informed HPV vaccination policy decisions in Canada and globally [66-68]. The model was calibrated to Canadian data on sexual behaviour and HPV epidemiology [7].

Two provinces with different vaccination coverage profiles were modelled: Québec (85% coverage with at least one dose in 2020) and Ontario (62-67% coverage with at least one dose in 2021). Historical changes in HPV vaccination strategies since the start of vaccination were included for the two provinces. From 2024 onward, the impact of switching to 1-dose vaccination was compared to remaining with the current provincial strategy and vaccination coverage.

The main outcomes were incidence of HPV-16 infection in females and males and cervical cancer incidence. Secondary outcomes included incidence of all other HPV-associated cancers in females and males, as well as number needed to vaccinate (NNV) to avert one cervical cancer case. The 1-dose best case scenario assumed non-inferiority of 1 versus 2 doses (VE = 98% and average VD = lifetime). Different pessimistic 1-dose scenarios (VE = 90% and/or VD = 30 or 25 years) were also evaluated. These best case and pessimistic scenarios were informed by 1-dose trial results and selected to illustrate the best and worst-case population-level impacts of switching to 1-dose vaccination to help inform decision-making.

HPV infections:

With 2-dose or non-inferior 1-dose vaccination, near elimination of HPV-16 infections in females and males was projected within the next 15 years, using vaccination coverage observed in Québec (85% vaccination coverage); and a greater than 90% reduction in infection incidence was projected using vaccination coverage observed in Ontario (where there has been 62 to 67% vaccination coverage). For the assumption of lower VE, 1-dose vaccination was projected to produce a similar population-level impact on HPV-16 infection compared to the non-inferior 2-dose vaccine scenario, though for the lower vaccination coverage estimate for Ontario, a small increase in HPV-16 infections was projected (3%). This occurs because herd-effects obtained through gender-neutral vaccination would mitigate the impact of reduced VE for the highly vaccinated population scenario considered in the model. Pessimistic scenarios were modelled assuming an average vaccine duration of protection of 25 to 30 years, with vaccine protection initially remaining stable before dropping rapidly, such that all vaccinated people were no longer protected 35-40 years after vaccination. In the most pessimistic scenario, where average duration of vaccine protection of 25 years was modelled (VD=25 years), 1-dose vaccination was projected to lead to a 20 to 27% rebound in HPV-16 infections starting 20 to 25 years after the switch to 1-dose

vaccination programs. Compared to the 25 years of vaccine duration of protection, rebound was projected to be smaller and to occur later when the 1-dose duration of protection lasting 30 years was modelled (i.e., 14 to 20% increase).

HPV-related cancers:

Compared to HPV infections, a smaller and later rebound in cervical cancer cases was projected for the 1-dose pessimistic duration of protection scenarios. This happens because, even if vaccine protection declines over time following 1-dose vaccination, vaccinated people are protected from infection for 25 to 30 years on average, and the average age at which people get HPV infections is older than the average age that people would get HPV infections in the absence of vaccination programs. Because people are older when they get infected in the model's pessimistic 1-dose vaccination scenarios compared to no vaccination, this reduces the number of years remaining after infection to develop cervical cancer. Despite the projected increases in incidence of cervical cancer in some of the pessimistic scenarios, all 1-dose scenarios were projected to still achieve cervical cancer elimination by 2040 in Quebec and 2050 in Ontario, using the WHO elimination threshold of an annual age-standardized incidence of 4 cervical cancer cases per 100,000 women.

Compared to incidence of cervical cancer, rebound in other HPV-associated cancers was more limited and delayed in the pessimistic 1-dose vaccination scenarios. This was due to the shift to older ages at infection which has a greater impact for other HPV-associated cancers, given their slower progression compared to cervical cancer.

If 1-dose protection is shown to wane substantially in the next 10 years, modelling showed that switching back to 2-dose routine vaccination after 10 years of one-dose vaccination could mitigate losses in HPV-associated cancer prevention, leading to similar numbers of cancers averted as remaining with 2-dose vaccination.

In terms of efficiency, the model projects that gender-neutral 1-dose routine vaccination would be more efficient than 2-dose routine vaccination, even for the most pessimistic 1-dose scenarios. Compared to no vaccination, the number of doses needed to prevent 1 cervical cancer case in the modelled population varied between 937 and 1,012 in Quebec and between 768 and 819 in Ontario, for the different 1-dose scenarios. The incremental NNVs for 2-dose vaccination compared to 1-dose vaccination were greater than 10,000 for all VE and VD scenarios considered.

These findings were robust in sensitivity analyses that explored the impact of uncertainty related to the duration of 1-dose protection and sexual activity in older adults. Additional work is required to better understand the progression rate and dynamics for other HPV-associated cancers and among equity-deprived populations.

VI. ETHICS, EQUITY, FEASIBILITY AND ACCEPTABILITY CONSIDERATIONS

VI.1 Ethics considerations

Transparent communication of justifications for updated recommendations with provinces and territories, as well as acknowledgement of any unknowns on the evidence of a 1-dose HPV vaccine schedule, will be crucial for the success of any changes to HPV immunization programs.

It is widely accepted that a 2- or 3-dose HPV vaccine schedule is anticipated to confer long-term (e.g., lifelong) duration of protection. This is based on both clinical trial data and population level studies, with greatest evidence for 2vHPV and 4vHPV vaccines since the first HPV vaccines became available in 2007. While evidence on the clinical benefits of a 1-dose HPV vaccine schedule is substantial, longer-term follow up (e.g., beyond 11 years) is limited. It is important for this uncertainty to be acknowledged. In addition, there remains uncertainty given limitations to real-time data on HPV-associated cancer rates and vaccine administration among equity-denied groups in Canada.

All Canadian provinces and territories have long-standing, publicly funded, school-based immunization programs for HPV. However, many children and adolescents remain unvaccinated, with recent estimates of vaccine coverage remaining below the national target of 90% by 17 years of age (See section III.5 Table 1). Additionally, regional data indicates variation of HPV vaccination rates at the local level [46]. Provinces and territories should consider offering the vaccine to individuals who declined/missed opportunities for vaccination during school-based programs. Consent of those under 18 years of age varies by Canadian jurisdiction; it is important for an individual to have agency in choosing whether to receive protection against HPV-associated cancers and other serious associated diseases.

VI.2 Equity considerations

Implementation of a 1-dose HPV immunization policy should include specific measures to enhance vaccine access, especially for equity-denied groups including Indigenous populations. The availability and frequency of immunization clinics for under-vaccinated populations should not decrease following adoption of a one-dose HPV vaccine program, as this may lead to decreased vaccination for those already facing health disparities related to HPV-associated diseases.

Recent data on vaccine uptake shows that certain areas (e.g., rural and remote populations) have lower vaccination and higher cervical cancer rates [46]. Specifically, First Nations, Métis, or Inuit populations in Canada experience higher rates of HPV infection and associated disease, as well

as lower cervical cancer screening rates, which can be complicated by stigmatization and discrimination when accessing healthcare [69]. Of note, recent Canadian data reports that Indigenous women are 2-20 times more likely to be diagnosed with cervical cancer compared to non-Indigenous women and have a mortality rate from cervical cancer 4 times higher than non-Indigenous women [70-73]. Immigrant and refugee populations in Canada also have lower cervical cancer screening and higher HPV infection rates, putting them at increased risk of HPV-associated morbidity and mortality. Further, studies reveal sub-provincial and inter-sociodemographic variation in HPV vaccination rates linked to social and/or material deprivation [46]. Intersectionality among residence, race, and socioeconomic status may further compound health inequities. Provincial and territorial efforts to increase vaccine access and uptake for equity-denied groups will be needed to mitigate any worsening of health disparities if there is a shift to a 1-dose HPV immunization program. Mitigation strategies that could promote equity include tailored catch-up programs, expanded publicly funded vaccine access such as in primary care and pharmacy settings, additional school-based clinics, simplified consent approaches, and reallocation of resources for doses to populations made vulnerable. Several studies conducted in Canada and other countries have found that school-based vaccination is the best strategy to support a reduction in health inequities [74-76].

VI.3 Feasibility considerations

In the short-term (i.e., within 10 years), a 1-dose schedule is expected to simplify immunization clinic delivery and has already been implemented in other countries, including the U.K. and Australia. In the long-term (i.e., beyond 10 years), a Canadian modeling study on the impact of HPV vaccination schedules on future disease burden indicates that all 1-dose scenarios could achieve cervical cancer elimination by 2040 in Quebec and 2050 in Ontario, under the WHO threshold (4 cervical cancers/100,000 woman-years) [7, 77].

VI.4 Acceptability considerations

Evidence is limited on the acceptability of a 1-dose HPV vaccine schedule in Canada; however, other international guidance bodies have issued off-label recommendations on a 1-dose schedule. Previous changes to the recommended HPV vaccine schedule in Canada from a 3-dose schedule to 2-3 doses for those starting their series who are younger than 15 years, was widely accepted and did not result in reduced vaccination rates. Similarly, a 1-dose policy may be perceived as

more acceptable by the general population due to its convenience and potential for fewer AEs following immunization compared to a 2 to 3 dose schedule.

VII. ECONOMICS

NACI guidance development should include a consideration of economic evidence to support proposed immunization guidance. At this time, not all policy questions are prioritized for Canadian-specific cost-effectiveness analyses [78]. Since the cost-effectiveness of reduced dose schedules for HPV vaccination programs has been documented and NACI was asked to consider a reduction of the recommended number of doses for HPV vaccine schedules, cost-effectiveness was not identified as a major determinant for the recommendation [79]. Specifically, a reduction in the number of recommended doses would be expected to reduce vaccine purchase and administration costs [80].

While an economic evaluation of the impact of a 1-dose HPV immunization program in Canada was not conducted, the potential population-level impact of switching to a 1-dose routine HPV vaccination program in Canada was evaluated (see section V. Disease Modeling). NACI also reviewed published economic evaluations comparing 1- versus 2-dose HPV vaccination schedules in high-income settings. Briefly, economic evidence from a previous review [79] was supplemented by a literature search in PubMed and MedRXiv of economic evaluations comparing 1- and multi-dose HPV vaccination programs published between January 1, 2022, and August 30, 2023. Key search terms included “HPV”, “vaccine”, “one-dose”, and “cost”. The review focused on studies in high-income countries to ensure relevance to the Canadian setting and excluded studies comparing 1-dose programs to no HPV vaccination or placebo. The search was limited to documents in English or French. There were no restrictions on the gender or age of the study population. Three relevant studies were identified.

The two studies that used estimates of vaccine effectiveness and duration of protection consistent with available data showed that most of the health benefits of 2-dose vaccination are achievable with one dose, with a 1-dose program expected to be cost-effective [80, 81]. These studies looked at vaccination in girls only. A third industry-funded study looking at vaccination in girls and boys suggested that a 1-dose program was unlikely to be cost-effective compared to a 2-dose program; however, this model used more pessimistic assumptions that are inconsistent with available empirical data [82, 83].

VIII. RECOMMENDATIONS

Recommendations for public health program level decision-making

(i.e., provinces/territories making decisions for publicly funded immunization programs)

1. **NACI continues to recommend HPV vaccination for all individuals 9 to 26 years of age.**

   (*Strong NACI recommendation)*

   Summary of evidence and rationale:

   - Without vaccination, it is estimated that 75% of people in Canada will acquire an HPV infection in their lifetime. HPV infection can lead to numerous cancers, including some that have been increasing in incidence in recent years, along with AGW. HPV is also associated with a rare but serious condition called recurrent respiratory papillomatosis (RRP).
   - HPV vaccine is most effective when given at a younger age, before exposure to HPV.
   - HPV vaccination is also expected to benefit those already exposed to some HPV types, as it provides protection against all the HPV types included in the vaccine.
   - HPV immunization coverage among adolescents and young adults varies across Canada; individuals who missed routine HPV immunization will remain at risk of HPV-associated diseases and can still benefit from HPV vaccination.
   - Increasing HPV vaccination coverage will provide the greatest herd immunity benefits to everyone. Immunization programs should strive to achieve high coverage to ensure the greatest population benefits.
   - High coverage will provide protective effects to those most vulnerable, including equity-denied groups and individuals who are immunocompromised. Immunization programs should monitor and address vaccination coverage among sub-groups, especially populations made vulnerable, and provide tailored efforts to improve coverage.
   - This strong NACI recommendation was originally issued in 2007 following authorization of 4vHPV in females ages 9 to 26 years, and was updated to include males ages 9 to 26 years in 2012 following expanded licensure.

Additional considerations on HPV vaccines and pregnancy:

- HPV infection during pregnancy may lead to adverse outcomes to the pregnant woman or pregnant individual and to the fetus.
- The HPV vaccine is expected to provide a benefit to anyone who is at ongoing risk of HPV infection, including during pregnancy.
- Evidence to date demonstrates no increased risk of adverse pregnancy or fetal outcomes associated with HPV vaccination during pregnancy. There is no known evidence nor biological mechanism to expect an increased risk of adverse pregnancy or fetal outcomes with HPV vaccination during pregnancy.
- Based on the above considerations, HPV vaccines can be offered in pregnancy.
- Routine questioning about last menstrual period or pregnancy is not required or recommended before offering HPV vaccine.

2. **NACI recommends that individuals 9 to 20 years of age should receive 1 dose of HPV vaccine, and individuals 21 to 26 years of age should receive 2 doses of HPV vaccine.**

   (*Strong NACI recommendation*)

   Summary of evidence and rationale:

   - A 1-dose schedule is highly effective against HPV infection based on available evidence, which is currently limited to studies in females, with current follow-up extending to 11 years following vaccination.
   - Most studies of a 1-dose schedule have been conducted in younger (e.g., 9-20 years of age) populations. Randomized controlled trial evidence has demonstrated that a 1-dose schedule is highly effective in preventing persistent HPV infection for up to 3 years among females 15 to 20 years of age, consistent with cohort studies that have reported findings up to 11 years.
   - Infectious disease modelling shows that under most assumptions, a one-dose strategy in Canada is expected to have similar health outcomes over the short and long term compared to a 2-dose strategy.
   - Published model-based economic assessments suggest that most of the health benefits of 2-dose vaccination are achievable with a 1-dose schedule and that a 1-dose HPV vaccine program may be cost-effective compared to 2-dose vaccination.
   - Currently, a 1-dose schedule is off-label for HPV vaccines. Manufacturer-led clinical trials in males and females to evaluate the efficacy and durability of 1-dose HPV vaccine schedules compared to a 3-dose schedule are commencing. Additionally, ongoing studies evaluating 1-dose HPV vaccine schedules will provide longer follow-up data in coming years.
   - Antibody responses to HPV vaccination are impacted by the number of vaccine doses received, however as there is no known immunological correlate of protection for the HPV vaccine for any clinical outcome, the clinical significance of such differences are unknown. Compared to natural infection, a 1-dose HPV vaccine schedule induces a higher antibody response. A second or third dose of HPV vaccine further increases antibody titers compared to a single vaccine dose. However, over time, antibody titers induced by vaccination stabilize to similar levels regardless of the number of doses received. Additionally, several studies have reported similar antibody avidity among individuals who received 1, 2, or 3 doses of HPV vaccines.
   - A 2-dose schedule may be considered on an individual basis for individuals 9 to 20 years of age with their health care provider. When 2 doses are offered, doses should be administered at least 24 weeks apart.

Additional considerations:

Individuals considered immunocompromised and individuals living with HIV:

- NACI reiterates its current guidance recommending a 3-dose schedule for individuals who are considered immunocompromised, as well as individuals living with HIV.

- See the Canadian Immunization Guide for additional guidance.

Surveillance and Monitoring

- Immunization programs should aim to maximize 1-dose coverage with emphasis on additional outreach to populations that currently have lower vaccine coverage. High HPV vaccine coverage will protect people (e.g., immunocompromised or those facing health inequities) through herd immunity.
- Surveillance activities to monitor the impact of changes to HPV vaccination schedules on HPV vaccine coverage should be prioritized by provinces, territories and local health authorities. Routine surveillance of coverage within school-based immunization and catch-up programs should support monitoring populations with lower vaccine coverage, with an emphasis on equity-denied groups, and focus delivery efforts on populations who are under-immunized. Surveillance should also differentiate and address low coverage areas within communities. Variations in coverage among rural and urban neighbourhoods, and within urban neighbourhoods, has been observed.
- Monitoring of vaccine confidence and interventions to improve HPV vaccination coverage should also be prioritized.
- Monitoring should include both HPV infection and disease outcomes from provinces and territories.
- NACI will continue to monitor evidence of 1-dose HPV vaccine schedules including long term durability (e.g., 20+ years follow-up time) as evidence becomes available from clinical trials, Canadian data, and other countries where similar schedules are adopted, and will issue updates to guidance as warranted.

HPV infection and cancer screening

- NACI emphasizes the ongoing need for additional public health measures such as HPV infection and associated cancers screening and surveillance and early access to treatment to prevent HPV-associated diseases for all Canadians. Trends in HPV infection incidence or the incidence of HPV-associated outcomes will be important to monitor in relation to any changes to HPV vaccine immunization programs.
- NACI also encourages dedicated efforts to implement such measures to equity-denied groups including First Nations, Inuit and Métis, some of whom face disproportionately high rates of HPV-associated cancers, and lower rates of HPV immunization. Continuing to provide HPV vaccination in school-based programs has been shown to reduce health inequities.

3. **Nonavalent 9vHPV vaccine should be used as it provides protection against the greatest number of HPV types and associated diseases.**

   (*Strong NACI recommendation*)

Recommendations for individual level decision-making

(i.e., healthcare providers advising individual clients)

4. **Individuals 27 years of age and older may receive the HPV vaccine with shared decision making and discussion with a healthcare provider. The vaccine should be given as a 2-dose schedule with doses administered at least 24 weeks apart.**

   (*Discretionary NACI recommendation*)

   Summary of evidence and rationale:

   - HPV vaccination provides the most benefit before initial HPV exposure. Unvaccinated individuals 27 years of age and older can still benefit from HPV vaccination, and especially if there is risk of exposure (for example: new sexual partners), as most will not have been infected with all HPV types included in the HPV vaccine.
   - HPV immunization coverage among adolescents and young adults varies across Canada; individuals who missed routine HPV immunization will remain at risk for HPV-associated diseases and may benefit from the vaccine even at older ages.
   - While the HPV vaccine is authorized for individuals 9 to 45 years of age, those 45 years and older may benefit from off-label vaccination based on risk. Individuals who think they may benefit from HPV vaccination who are 45 years or older should consult their healthcare provider to discuss the potential benefits of HPV vaccination.
   - Evidence on a 1-dose schedule is currently limited to studies primarily in females aged 9 to 20 years.
   - Among individuals who are immunocompetent, there is sufficient evidence of comparable protection from 2 doses compared to 3 doses.
   - While NACI recommends a 2-dose HPV vaccination schedule for immunocompetent individuals 27 years of age and older, a 1-dose schedule is expected to provide clinical benefit. Clinical trials and real-world effectiveness studies are ongoing and will further evaluate the equivalency of 1- vs. 2-dose schedules.

   Additional considerations:

   - While not recommended at a population level, in discussion with their healthcare provider, individuals who have completed immunization with a different HPV vaccine (2vHPV or 4vHPV vaccines) and are at ongoing risk of HPV exposure, may benefit from one additional

dose of the 9vHPV vaccine to receive protection offered by the additional types included in the 9vHPV vaccine.

Table 3. NACI Recommendations on HPV Immunization Schedules

Group(s)	NACI Guidelines on HPV Immunization Schedules
9 to 20 years*	**1-dose** HPV vaccine schedule with 9vHPV.**
21 to 26 years*	**2-dose HPV vaccine schedule with 9vHPV; doses administered at least 24 weeks apart.**
27 years and older*	**2-dose HPV vaccine schedule with 9vHPV; doses administered at least 24 weeks apart.**
9 years and older* who are immunocompromised or living with HIV	**3-dose HPV vaccine schedule*** with 9vHPV.**

*Recommended schedule is based on age at initiation of vaccination.

**A 2-dose schedule may be considered on an individual basis for individuals 9 to 20 years of age. When 2 doses are offered, doses should be administered at least 24 weeks apart.

***Individuals recommended to receive HPV vaccine who are immunocompromised, including individuals living with HIV, should receive a 3-dose HPV vaccine schedule with a nonavalent HPV vaccine. The minimum interval between the first and second doses of vaccine is 4 weeks (1 month), the minimum interval between the second and third doses of vaccine is 12 weeks (3 months), and the minimum interval between the first and last doses is 24 weeks (6 months).

Refer to the CIG Human papillomavirus (HPV) vaccines chapter in Part 4 for additional guidance on recommended HPV vaccine schedules.

Table 4. NACI recommendations: Strength of recommendation

Strength of Recommendation	STRONG	DISCRETIONARY
Wording	"should/should not be offered"	"may/may not be offered"
Rationale	Known/anticipated advantages outweigh known/anticipated disadvantages ("should"), OR Known/Anticipated disadvantages	Known/anticipated advantages are closely balanced with known/anticipated disadvantages, OR uncertainty

	outweigh known/anticipated advantages (“should not”)	in the evidence of advantages and disadvantages exists
Implication	A strong recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present.	A discretionary recommendation may be considered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

IX. RESEARCH PRIORITIES

Research to address the following outstanding questions is encouraged:

1. Continuous monitoring of the immunogenicity, efficacy, effectiveness and duration of protection of a 1-dose HPV vaccine schedule, through both clinical trials and real-world monitoring.
2. Population-based studies to evaluate the epidemiology of HPV and associated diseases in Canada, as well as any potential changes to the epidemiology.
3. Population-based studies specifically aimed at evaluating the burden of disease among populations who face health inequities (including persons living in remote/northern communities, First Nations, Inuit and Métis, individuals experiencing material and social deprivation, and recent immigrants).
4. Population-based studies specifically aimed at evaluating the impact of a 1-dose HPV vaccine schedule in vaccine acceptance and uptake in under-vaccinated groups.
5. Evidence-informed strategies to enhance HPV vaccine equity in Canada.
6. Further evaluation of the immunogenicity, efficacy and/or effectiveness of a 1-dose HPV vaccine schedule on HPV infections that are not of the cervix.
7. Further evaluation on the safety and effectiveness of HPV vaccination during pregnancy, specifically with regard to the timing of vaccination during the pregnancy.
8. Monitoring of HPV type-specific epidemiology across Canada, as HPV screening programs are implemented by provinces and territories.

ABBREVIATIONS

AE	Adverse events
AGW	Anogenital warts
CAEFISS	Canadian Adverse Events Following Immunization Surveillance System
CCDR	Canada Communicable Disease Report
CCS	Canadian Cancer Society
CI	Confidence interval
CIG	Canadian Immunization Guide
CIN	Cervical intraepithelial neoplasia
COVID-19	Coronavirus disease 2019
DNA	Deoxyribonucleic acid
EEFA	Ethics, equity, feasibility, acceptability
EtD	Evidence to decision
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
2vHPV	CERVARIX ® vaccine
4vHPV	GARDASIL ® vaccine
9vHPV	GARDASIL ® 9 vaccine
JoRRP	Juvenile onset recurrent respiratory papillomatosis
NACI	National Advisory Committee on Immunization
PHAC	Public Health Agency of Canada

RCT	Randomized control trial
RRP	Recurrent respiratory papillomatosis
SAGE	Strategic Advisory Group on Experts
VD	Duration of vaccine protection
VE	Vaccine efficacy
WHO	World Health Organization

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NACI HPV Working Group

Members: V Dubey (WG Chair) N Audet, C Elwood, M Halligan, L Markowitz, M O'Driscoll, G Oglivie, C Sauvageau and S Wilson.

NACI

NACI Members: R Harrison (Chair), V Dubey (Vice-Chair), M Andrew, J Bettinger, N Brousseau, A Buchan, H Decaluwe, P De Wals, E Dubé, K Hildebrand, K Klein, M O'Driscoll, J Papenburg, A Pham-Huy, B Sander, and S Wilson.

Liaison Representatives: L Bill/ M Nowgesic (Canadian Indigenous Nurses Association), LM Bucci (Canadian Public Health Association), S Buchan (Canadian Association for Immunization Research, Evaluation and Education) E Castillo (Society of Obstetricians and Gynaecologists of Canada), J Comeau (Association of Medical Microbiology and Infectious Disease Control), M Lavoie (Council of Chief Medical Officers of Health), J MacNeil (Center for Disease control and Prevention), M McIntyre (Canadian Nurses Association), D Moore (Canadian Paediatric Society), M Osmack (Indigenous Physicians Association of Canada), J Potter (College of Family Physicians of Canada), D Singh (Canadian Immunization Committee), and A Ung (Canadian Pharmacists Association).

Ex-officio Representatives: V Beswick-Escanlar (National Defence and the Canadian Armed Forces), E Henry (Centre for Immunization Programs, PHAC), M Lacroix (Public Health Ethics Consultative Group, PHAC), P Fandja (Marketed Health Products Directorate, Health Canada), M Maher (Centre for Immunization Surveillance, PHAC), C Pham (Biologic and Radiopharmaceutical Drugs Directorate, Health Canada), M Routledge (National Microbiology Laboratory, PHAC), M Su (COVID-19 Epidemiology and Surveillance, PHAC), and T Wong (First Nations and Inuit Health Branch, Indigenous Services Canada).

REFERENCES

1. Canadian Immunization Committee. Summary of Canadian Immunization Committee (CIC) recommendations for human papillomavirus immunization programs. CCDR. 2014 Apr 17;40(8). https://doi.org/10.14745/ccdr.v40i08a02.

2. Canadian Partnership Against Cancer. Canadian Strategy for Cancer Control [Internet]. Canadian Partnership Against Cancer; 2019 [cited 2024 Apr 25]. Available from: https://s22457.pcdn.co/wp-content/uploads/2019/06/Canadian-Strategy-Cancer-Control-2019-2029-EN.pdf.

3. Public Health Agency of Canada. Vaccination Coverage Goals and Vaccine Preventable Disease Reduction Targets by 2025 [Internet]. Ottawa (ON): Government of Canada; 2022 Aug 16 [cited 2024 Apr 24]. Available from: https://www.canada.ca/en/public-health/services/immunization-vaccine-priorities/national-immunization-strategy/vaccination-coverage-goals-vaccine-preventable-diseases-reduction-targets-2025.html.

4. Canadian Partnership Against Cancer. Action plan for the elimination of cervical cancer in Canada, 2020–2030 [Internet]. Toronto (ON): Canadian Partnership Against Cancer; 2021 [cited 2024 Apr 24]. Available from: https://www.partnershipagainstcancer.ca/topics/elimination-cervical-cancer-action-plan/.

5. Public Health Agency of Canada. Highlights from the 2021 childhood National Immunization Coverage Survey (cNICS) [Internet]. Ottawa (ON): Government of Canada; 2023 Jun 12 [cited 2024 Apr 24]. Available from: https://www.canada.ca/en/public-health/services/immunization-vaccines/vaccination-coverage/2021-highlights-childhood-national-immunization-coverage-survey.html.

6. World Health Organization. WHO updates recommendations on HPV vaccination schedule [Internet]. U.S.: WHO; 2022 Dec 22 [cited 2024 May 29]. Available from: https://www.who.int/news/item/20-12-2022-WHO-updates-recommendations-on-HPV-vaccination-schedule.

7. Drolet M, Laprise J, Chamberland E, Sauvageau C, Wilson S, Lim GH, et al. Potential impact of switching from a two- to one-dose gender-neutral routine HPV vaccination program in Canada: a mathematical modeling analysis. medRxiv. 2024 May 29:2024.05.29.24308112. https://doi.org/10.1101/2024.05.29.24308112.

8. Ismail SJ, Hardy K, Tunis MC, Young K, Sicard N, Quach C. A framework for the systematic consideration of ethics, equity, feasibility, and acceptability in vaccine program recommendations. Vaccine. 2020 Aug 10;38(36). https://doi.org/10.1016/j.vaccine.2020.05.051.

9. National Advisory Committee on Immunization. National Advisory Committee on Immunization (NACI): Methods and process [Internet]. Ottawa (ON): Government of Canada; 2023 Apr 12

[cited 2024 Apr 24]. Available from: https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/methods-process.html.

10. Ardekani A, Taherifard E, Mollalo A, Hemadi E, Roshanshad A, Fereidooni R, et al. Human papillomavirus infection during pregnancy and childhood: a comprehensive review. Microorganisms. 2022 Sep 28;10(10):1932. https://doi.org/10.3390/microorganisms10101932.

11. Condrat CE, Filip L, Gherghe M, Cretoiu D, Suciu N. Maternal HPV infection: effects on pregnancy outcome. Viruses. 2021 Dec 07;13(12):2455. https://doi.org/10.3390/v13122455.

12. Niyibizi J, Zanré N, Mayrand M, Trottier H. Association between maternal human papillomavirus infection and adverse pregnancy outcomes: systematic review and meta-analysis. J Infect Dis. 2020 Jun 15;221(12):1925-37. https://doi.org/10.1093/infdis/jiaa054.

13. Canadian Cancer Society. Human papillomavirus [Internet]. Canadian Cancer Society; 2024 [cited 2024 Apr 24]. Available from: https://cancer.ca/en/cancer-information/reduce-your-risk/get-vaccinated/human-papillomavirus-hpv.

14. Salvadori MI. Human papillomavirus vaccine for children and adolescents. Pediatrics & Child Health. 2018 Jun 12:262-5. https://doi.org/10.1093/pch/pxx179.

15. Canadian Partnership Against Cancer. HPV immunization for the prevention of cervical cancer [Internet]. Toronto (ON): Canadian Partnership Against Cancer; 2021 Mar [cited 2024 Apr 24]. Available from: https://s22457.pcdn.co/wp-content/uploads/2021/04/HPV-immunization-prevention-cervical-cancer-EN.pdf.

16. Bruni L., Albero G, Serrano B, Mena M, Collado JJ, Gomez D, et al. Human Papillomavirus and Related Diseases in Canada. Summary Report [Internet]. Barcelona (ES): ICO/IARC Information Centre on HPV and Cancer; 2023 Mar 10 [cited 2024 Apr 24]. Available from: https://hpvcentre.net/statistics/reports/CAN.pdf.

17. 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. 2015 Apr 29;107(6):djv086. https://doi.org/10.1093/jnci/djv086.

18. de Sanjose S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010 Nov;11(11):1048-56. https://doi.org/10.1016/S1470-2045(10)70230-8.

19. Joura EA, Ault KA, Bosch FX, Brown D, Cuzick J, Ferris D, et al. Attribution of 12 high-risk human papillomavirus genotypes to infection and cervical disease. Cancer Epidemiol Biomarkers Prev. 2014 Oct;23(10):1997-2008. https://doi.org/10.1158/1055-9965.EPI-14-0410.

20. Merck. GARDASIL®9 FAQs [Internet]. U.S.: Merck; 2022 [cited 2024 Apr 25]. Available from: https://www.gardasil9.ca/faq/.

21. Canadian Cancer Society. Cervical cancer statistics [Internet]. Canadian Cancer Society; 2023 Nov [cited 2024 Apr 25]. Available from: https://cancer.ca/en/cancer-information/cancer-types/cervical/statistics.

22. Habbous S, Chu KP, Lau H, Schorr M, Belayneh M, Ha MN, et al. Human papillomavirus in oropharyngeal cancer in Canada: analysis of 5 comprehensive cancer centres using multiple imputation. CMAJ. 2017 Aug 14;189(32):E1030-40. https://doi.org/10.1503/cmaj.161379.

23. Canadian Research Data Centre Network. Canadian Cancer Registry [Internet]. Hamilton (ON): Canadian Research Data Centre Network; 2020 [cited 2024 Apr 30]. Available from: https://crdcn.ca/publications-data/data/.

24. Centers for Disease Control and Prevention. HPV and Oropharyngeal Cancer [Internet]. U.S.: Centers for Disease Control and Prevention; 2023 Sep 12 [cited 2024 Apr 25]. Available from: https://www.cdc.gov/cancer/hpv/basic_info/hpv_oropharyngeal.htm.

25. Nichols AC, Palma DA, Dhaliwal SS, Tan S, Theuer J, Chow W, et al. The epidemic of human papillomavirus and oropharyngeal cancer in a Canadian population. Curr Oncol. 2013 Aug;20(4):212-9. https://doi.org/10.3747/co.20.1375.

26. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010 Jul 01;363(1):24-35. https://doi.org/10.1056/NEJMoa0912217.

27. Nichols AC, Dhaliwal SS, Palma DA, Basmaji J, Chapeskie C, Dowthwaite S, et al. Does HPV type affect outcome in oropharyngeal cancer? J Otolaryngol Head Neck Surg. 2013 Feb 01;42(1):9. https://doi.org/10.1186/1916-0216-42-9.

28. Landy R, Haber G, Graubard BI, Campos NG, Sy S, Kim JJ, et al. Upper age limits for US male human papillomavirus vaccination for oropharyngeal cancer prevention: a microsimulation-based modeling study. J Natl Cancer Inst. 2023 Apr 11;115(4):429-36. https://doi.org/10.1093/jnci/djad009.

29. Lingen MW, Abt E, Agrawal N, Chaturvedi AK, Cohen E, D'Souza G, et al. Evidence-based clinical practice guideline for the evaluation of potentially malignant disorders in the oral cavity: A report of the American Dental Association. J Am Dent Assoc. 2017 Oct;148(10):712,727.e10. https://doi.org/10.1016/j.adaj.2017.07.032.

30. Prigge ES, von Knebel Doeberitz M, Reuschenbach M. Clinical relevance and implications of HPV-induced neoplasia in different anatomical locations. Mutat Res Rev Mutat Res. 2017 Jun;772:51-66. https://doi.org/10.1016/j.mrrev.2016.06.005.

31. Hawkins RJ, Wang EE, Leake JL. Preventive health care, 1999 update: prevention of oral cancer mortality. The Canadian Task Force on Preventive Health Care. J Can Dent Assoc. 1999 Dec;65(11):617. https://doi.org/https://www.cda-adc.ca/jcda/vol-65/issue-11/617.html.

32. World Health Organization. One in three men worldwide are infected with genital human papillomavirus [Internet]. U.S.: World Health Organization; 2023 Sep 01 [cited 2024 Apr 24]. Available from: https://www.who.int/news/item/01-09-2023-one-in-three-men-worldwide-are-infected-with-genital-human-papillomavirus.

33. Kliewer EV, Demers AA, Elliott L, Lotocki R, Butler JRG, Brisson M. Twenty-year trends in the incidence and prevalence of diagnosed anogenital warts in Canada. Sex Transm Dis. 2009 Jun;36(6):380-6. https://doi.org/10.1097/OLQ.0b013e318198de8c.

34. Thomas R, Steben M, Greenwald Z, Stutz M, Rodier C, DeAngelis F, et al. Recurrence of human papillomavirus external genital wart infection among high-risk adults in Montréal, Canada. Sex Transm Dis. 2017 Nov;44(11):700-6. https://doi.org/10.1097/OLQ.0000000000000666.

35. Lukac CD, Donken R, Otterstatter M, Mazo O, Wong S, Marra F, et al. Impacts of human papillomavirus immunization programs on rates of anogenital warts in British Columbia, Canada, 2000 to 2017. Sex Trans Dis. 2020 Oct;47(10):691. https://doi.org/10.1097/OLQ.0000000000001235.

36. Campisi P, Hawkes M, Simpson K. The epidemiology of juvenile onset recurrent respiratory papillomatosis derived from a population level national database. Laryngoscope. 2010 Jun;120(6):1233-45. https://doi.org/10.1002/lary.20901.

37. Benedict JJ, Derkay CS. Recurrent respiratory papillomatosis: A 2020 perspective. Laryngoscope Investig Otolaryngol. 2021 Apr;6(2):340-5. https://doi.org/10.1002/lio2.545.

38. Meites E, Stone L, Amiling R, Singh V, Unger ER, Derkay CS, et al. Significant declines in juvenile-onset recurrent respiratory papillomatosis following human papillomavirus (HPV) vaccine introduction in the United States. Clin Infect Dis. 2021 Sep 07;73(5):885-90. https://doi.org/10.1093/cid/ciab171.

39. Popescu SD, Boiangiu AG, Sima R, Bilteanu L, Vladareanu S, Vladareanu R. Maternal HPV infection and the estimated risks for adverse pregnancy outcomes-a systematic review. Diagnostics (Basel). 2022 Jun 15;12(6):1471. https://doi.org/10.3390/diagnostics12061471.

40. Gouvernement du Québec. Eligibility - Children in Grade 4 of primary school and Secondary 3 [Internet]. QC: Gouvernement du Québec; 2023 Jan 17 [cited 2024 May 30]. Available from: https://www.quebec.ca/en/health/advice-and-prevention/vaccination/human-papillomavirus-hpv-vaccination-program/eligibility.

41. Umar I., Albert M, Roerig M, Saragosa M, Allin S. Eligibility and out-of-pocket cost for HPV vaccines across Canada [Internet]. Toronto (ON): North American Observatory on Health Systems and Policies; 2022 Dec [cited 2024 Apr 25]. Available from: https://naohealthobservatory.ca/wp-content/uploads/2023/06/NAO-Rapid-Review-36_EN.pdf.

42. Canadian Partnership Against Cancer. HPV vaccine access in Canada, 2022 [Internet]. Toronto (ON): Canadian Partnership Against Cancer; 2022 [cited 2024 Apr 24]. Available from: https://www.partnershipagainstcancer.ca/cancer-strategy/.

43. Henderson RI, Shea-Budgell M, Healy C, Letendre A, Bill L, Healy B, et al. First nations people's perspectives on barriers and supports for enhancing HPV vaccination: foundations for sustainable, community-driven strategies. Gynecol Oncol. 2018 Apr;149(1):93-100. https://doi.org/10.1016/j.ygyno.2017.12.024.

44. Sell H, Assi A, Driedger SM, Dubé È, Gagneur A, Meyer SB, et al. Continuity of routine immunization programs in Canada during the COVID-19 pandemic. Vaccine. 2021 Sep 15;39(39):5532-7. https://doi.org/10.1016/j.vaccine.2021.08.044.

45. Sell H, Raj Paudel Y, Voaklander D, MacDonald SE. School immunization coverage in adolescents during the COVID-19 pandemic: a retrospective cohort study. Vaccine. 2023 Feb 10;41(7):1333-41. https://doi.org/10.1016/j.vaccine.2023.01.011.

46. Dionne M, Sauvageau C, Kiely M, Dahhou M, Hamel D, Rathwell M, et al. School-based vaccination program against HPV and hepatitis B: a longitudinal analysis of vaccine coverage between 2015 and 2021 in Quebec. Vaccine. 2024 Jan 01;42(1):17-23. https://doi.org/10.1016/j.vaccine.2023.11.055.

47. Barnabas RV, Brown ER, Onono MA, Bukusi EA, Njoroge B, Winer RL, et al. Durability of single-dose HPV vaccination in young Kenyan women: randomized controlled trial 3-year results. Nat Med. 2023 Dec;29(12):3224-32. https://doi.org/10.1038/s41591-023-02658-0.

48. Kreimer AR, Struyf F, Del Rosario-Raymundo MR, Hildesheim A, Skinner SR, Wacholder S, et al. Efficacy of fewer than three doses of an HPV-16/18 AS04-adjuvanted vaccine: combined analysis of data from the Costa Rica Vaccine and PATRICIA Trials. Lancet Oncol. 2015 Jul;16(7):775-86. https://doi.org/10.1016/S1470-2045(15)00047-9.

49. Basu P, Malvi SG, Joshi S, Bhatla N, Muwonge R, Lucas E, et al. Vaccine efficacy against persistent human papillomavirus (HPV) 16/18 infection at 10 years after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre, prospective, cohort study. Lancet Oncol. 2021 Nov;22(11):1518-29. https://doi.org/10.1016/S1470-2045(21)00453-8.

50. Kreimer AR, Sampson JN, Porras C, Schiller JT, Kemp T, Herrero R, et al. Evaluation of durability of a single dose of the bivalent HPV vaccine: the CVT trial. J Natl Cancer Inst. 2020 Feb 10;112(10):1038-46. https://doi.org/10.1093/jnci/djaa011.

51. Batmunkh T, Dalmau MT, Munkhsaikhan M, Khorolsuren T, Namjil N, Surenjav U, et al. A single dose of quadrivalent human papillomavirus (HPV) vaccine is immunogenic and reduces HPV detection rates in young women in Mongolia, six years after vaccination. Vaccine. 2020 Jun 02;38(27):4316-24. https://doi.org/10.1016/j.vaccine.2020.04.041.

52. Hariri S, Schuler MS, Naleway AL, Daley MF, Weinmann S, Crane B, et al. Human papillomavirus vaccine effectiveness against incident genital warts among female health-plan enrollees, United States. Am J Epidemiol. 2018 Feb 01;187(2):298-305. https://doi.org/10.1093/aje/kwx253.

53. Safaeian M, Porras C, Pan Y, Kreimer A, Schiller JT, Gonzalez P, et al. Durable antibody responses following one dose of the bivalent human papillomavirus L1 virus-like particle vaccine in the Costa Rica vaccine trial. Cancer Prev Res (Phila). 2013 Nov;6(11):1242-50. https://doi.org/10.1158/1940-6207.CAPR-13-0203.

54. Joshi S, Anantharaman D, Muwonge R, Bhatla N, Panicker G, Butt J, et al. Evaluation of immune response to single dose of quadrivalent HPV vaccine at 10-year post-vaccination. Vaccine. 2023 Jan 04;41(1):236-45. https://doi.org/10.1016/j.vaccine.2022.11.044.

55. Watson-Jones D, Changalucha J, Whitworth H, Pinto L, Mutani P, Indangasi J, et al. Immunogenicity and safety of one-dose human papillomavirus vaccine compared with two or three doses in Tanzanian girls (DoRIS): an open-label, randomised, non-inferiority trial. Lancet Glob Health. 2022 Oct;10(10):e1473-84. https://doi.org/10.1016/S2214-109X(22)00309-6.

56. Romero B, Herrero R, Porras C, Hildesheim A, Ocampo R. Durabiility of HPV-16/18 antibodies 16 years after a single dose of the bivalent HPV vaccine: the Costa Rica HPV vaccine trial [abstract presented at the 35th International Papillomavirus Conference April 21, 2023] [Internet]. Washington (DC): International Papillomavirus Society; 2023 Apr 21 [cited 2024 May 29]. Available from: https://info.kenes.com/Flip/IPVC23_IPVC%202023%20-%20Abstracts%20E-Book/.

57. Donken R, Dobson SRM, Marty KD, Cook D, Sauvageau C, Gilca V, et al. Immunogenicity of 2 and 3 doses of the quadrivalent human papillomavirus vaccine up to 120 months postvaccination: follow-up of a randomized clinical trial. Clin Infect Dis. 2020 Aug 14;71(4):1022-9. https://doi.org/10.1093/cid/ciz887.

58. Bornstein J, Roux S, Kjeld Petersen L, Huang L, Dobson SR, Pitisuttithum P, et al. Three-year follow-up of 2-dose versus 3-dose HPV vaccine. Pediatrics. 2021 Jan;147(1):e20194035. https://doi.org/10.1542/peds.2019-4035.

59. Leung TF, Liu AP, Lim FS, Thollot F, Oh HML, Lee BW, et al. Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and 4vHPV vaccine administered according to two- or three-dose schedules in girls aged 9-14 years: results to month 36 from a randomized trial. Vaccine. 2018 Jan 02;36(1):98-106. https://doi.org/10.1016/j.vaccine.2017.11.034.

60. Romanowski B, Schwarz TF, Ferguson L, Peters K, Dionne M, Behre U, et al. Sustained immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine administered as a two-dose schedule in adolescent girls: five-year clinical data and modeling predictions from a randomized study. Hum Vaccin Immunother. 2016 Jan;12(1):20-9. https://doi.org/10.1080/21645515.2015.1065363.

61. Merck Canada Inc. Product Monograph Including Patient Medication Information GARDASIL®9 [Human Papillomavirus 9-valent Vaccine, Recombinant] [Internet]. Kirkland (QC): Merck Canada Inc.; 2023 Jul 07 [cited 2024 Apr 29]. Available from: https://www.merck.ca/en/wp-content/uploads/sites/20/2021/04/GARDASIL_9-PM_E.pdf.

62. Moreira ED, Giuliano AR, de Hoon J, Iversen O-, Joura EA, Restrepo J, et al. Safety profile of the 9-valent human papillomavirus vaccine: assessment in prior quadrivalent HPV vaccine recipients and in men 16 to 26 years of age. Hum Vaccin Immunother. 2017 Dec 14;14(2):396-403. https://doi.org/10.1080/21645515.2017.1403700.

63. GlaxoSmithKline Inc. Product Monograph Including Patient Medication Information Cervarix Human Papillomavirus vaccine Types 16 and 18 (Recombinant, AS04 adjuvanted) [Internet]. Mississauga (ON): GlaxoSmithKline Inc.; 2023 Nov 09 [cited 2024 Apr 29]. Available from: https://ca.gsk.com/media/6236/cervarix.pdf.

64. Arbyn M, Xu L, Simoens C, Martin-Hirsch PP. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. Cochrane Database Syst Rev. 2018 May 09;5(5):CD009069. https://doi.org/10.1002/14651858.CD009069.pub3.

65. Yan X, Li H, Song B, Huang G, Chang Q, Wang D, et al. Association of periconceptional or pregnancy exposure of HPV vaccination and adverse pregnancy outcomes: a systematic review and meta-analysis with trial sequential analysis. Front Pharmacol. 2023 May 09;14:1181919. https://doi.org/10.3389/fphar.2023.1181919.

66. Van de Velde N, Boily M, Drolet M, Franco EL, Mayrand M, Kliewer EV, et al. Population-level impact of the bivalent, quadrivalent, and nonavalent human papillomavirus vaccines: a model-based analysis. J Natl Cancer Inst. 2012 Nov 21;104(22):1712-23. https://doi.org/10.1093/jnci/djs395.

67. Brisson M, Laprise J, Drolet M, Van de Velde N, Franco EL, Kliewer EV, et al. Comparative cost-effectiveness of the quadrivalent and bivalent human papillomavirus vaccines: a transmission-dynamic modeling study. Vaccine. 2013 Aug 20;31(37):3863-71. https://doi.org/10.1016/j.vaccine.2013.06.064.

68. Brisson M, Bénard É, Drolet M, Bogaards JA, Baussano I, Vänskä S, et al. Population-level impact, herd immunity, and elimination after human papillomavirus vaccination: a systematic review and meta-analysis of predictions from transmission-dynamic models. Lancet Public Health. 2016 Nov;1(1):e8-e17. https://doi.org/10.1016/S2468-2667(16)30001-9.

69. Turpel-Lalond ME. In Plain Sight: Addressing Indigenous-specific Racism and Discrimination in B.C. Health Care [Internet]. B.C.: Government of British Columbia; 2020 [cited 2024 Apr 29]. Available from: https://engage.gov.bc.ca/app/uploads/sites/613/2020/11/In-Plain-Sight-Full-Report-2020.pdf.

70. Dick A, Holyk T, Taylor D, Wenninger C, Sandford J, Smith L, et al. Highlighting strengths and resources that increase ownership of cervical cancer screening for Indigenous communities in Northern British Columbia: community-driven approaches. Int J Gynaecol Obstet. 2021 Nov;155(2):211-9. https://doi.org/10.1002/ijgo.13915.

71. Chiefs of Ontario, Cancer Care Ontario, Institute for Clinical Evaluative Sciences. Cancer in First Nations People in Ontario: Incidence, Mortality, Survival and Prevalence [Internet]. Toronto (ON): Cancer Care Ontario; 2017 [cited 2024 Apr 29]. Available from: https://www.cancercareontario.ca/sites/ccocancercare/files/assets/CancerFirstNationsReport_Accessible.pdf.

72. Canadian Partnership Against Cancer. Canada acts to meet WHO Call to eliminate cervical cancer [Internet]. Toronto (ON): Canadian Partnership Against Cancer; 2020 Feb 04 [cited 2024 Apr 29]. Available from: https://www.partnershipagainstcancer.ca/news-events/news/article/eliminate-cervical-cancer/.

73. Ahmed S, Shahid RK, Episkenew JA. Disparity in cancer prevention and screening in aboriginal populations: recommendations for action. Curr Oncol. 2015 Dec;22(6):417-26. https://doi.org/10.3747/co.22.2599.

74. Bird Y, Obidiya O, Mahmood R, Nwankwo C, Moraros J. Human papillomavirus vaccination uptake in Canada: a systematic review and meta-analysis. Int J Prev Med. 2017 Sep 14;8:71. https://doi.org/10.4103/ijpvm.IJPVM_49_17.

75. Shapiro GK, Tatar O, Knäuper B, Griffin-Mathieu G, Rosberger Z. The impact of publicly funded immunization programs on human papillomavirus vaccination in boys and girls: an observational study. Lancet Reg Health Am. 2022 Apr;8:100128. https://doi.org/10.1016/j.lana.2021.100128.

76. Wang J, Ploner A, Sparén P, Lepp T, Roth A, Arnheim-Dahlström L, et al. Mode of HPV vaccination delivery and equity in vaccine uptake: a nationwide cohort study. Prev Med. 2019 Mar;120:26-33. https://doi.org/10.1016/j.ypmed.2018.12.014.

77. World Health Organization. Global strategy to accelerate the elimination of cervical cancer as a public health problem [Internet]. U.S.: World Health Organization; 2020 [cited 2024 Apr 29]. Available from: https://iris.who.int/bitstream/handle/10665/336583/9789240014107-eng.pdf?sequence=1.

78. Public Health Agency of Canada. Process for incorporating economic evidence into federal vaccine recommendations: National Advisory Committee on Immunization (NACI) [Internet].

Ottawa (ON): Government of Canada; c2023. Economic process in detail; 2023 Aug 02 [cited 2024 Apr 30]. Available from: https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/methods-process/incorporating-economic-evidence-federal-vaccine-recommendations.html.

79. PATH. Review of the current published evidence for single-dose HPV vaccination 4th edition [Internet]. PATH; 2022 May 30 [cited 2024 Apr 30]. Available from: https://media.path.org/documents/20220328_SDHPV_Evidence_Review_Edition_4_Final_L2.pdf?_gl=1*1fnex6o*_ga*MTk0OTE3MDk0NS4xNzAyMzk1MzA3*_ga_YBSE7ZKDQM*MTcxNzQyMzQxMy4yLjEuMTcxNzQyMzQyNS40OC4wLjA.*_gcl_au*MTg2Njk4Mzc2OC4xNzE3NDIzNDE0.

80. Prem K, Choi YH, Bénard É, Burger EA, Hadley L, Laprise J, et al. Global impact and cost-effectiveness of one-dose versus two-dose human papillomavirus vaccination schedules: a comparative modelling analysis. BMC Med. 2023 Aug 28;21(1):313. https://doi.org/10.1186/s12916-023-02988-3.

81. Jit M, Brisson M, Laprise J, Choi YH. Comparison of two dose and three dose human papillomavirus vaccine schedules: cost effectiveness analysis based on transmission model. BMJ. 2015 Jan 06;350:g7584. https://doi.org/10.1136/bmj.g7584.

82. Daniels V, Saxena K, Patterson-Lomba O, Gomez-Lievano A, Saah A, Luxembourg A, et al. Modeling the health and economic implications of adopting a 1-dose 9-valent human papillomavirus vaccination regimen in a high-income country setting: an analysis in the United Kingdom. Vaccine. 2022 Mar 25;40(14):2173-83. https://doi.org/10.1016/j.vaccine.2022.02.067.

83. Burger E, Baussano I, Kim JJ, Laprise J, Berkhof J, Schiller JT, et al. Recent economic evaluation of 1-dose HPV vaccination uses unsupported assumptions. Vaccine. 2023 Apr 17;41(16):2648-9. https://doi.org/10.1016/j.vaccine.2022.07.022.