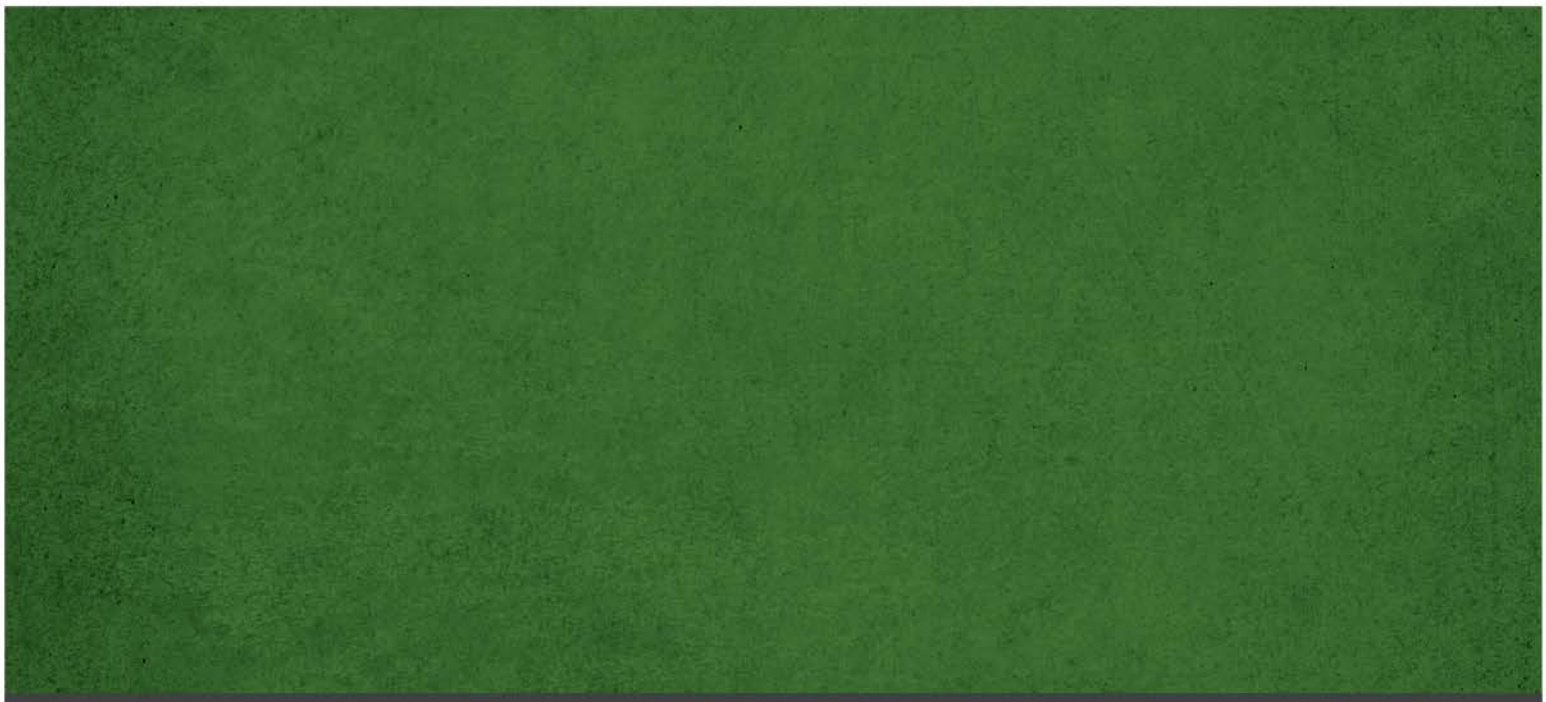
An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

Updated Recommendations on Human Papillomavirus (HPV) Vaccines: 9-valent HPV vaccine 2-dose immunization schedule and the use of HPV vaccines in immunocompromised populations



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PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (hereafter referred to as PHAC) with ongoing and timely medical, scientific, and public health advice relating to immunization. PHAC acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) 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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SUMMARY OF INFORMATION CONTAINED IN THIS NACI STATEMENT

The following summary highlights key information for immunization providers. Please refer to the remainder of the Statement for details.

1. What

Human papillomavirus (HPV) infections are the most common sexually transmitted infections. There are over 100 types of HPV, and they are broadly classified into high and low risk types.

High-risk HPV types can lead to cervical and anogenital cancers, as well as certain cancers of the head and neck. Low-risk HPV types can cause condylomata acuminata, also called anogenital warts (AGWs).

Gardasil® (HPV4 vaccine) has been authorized for use in Canada since 2006 for the prevention of HPV types 6 and 11 -related AGWs and HPV types 16 and 18 -related cancers. Cervarix® (HPV2 vaccine) has been authorized for use in Canada since 2010 for the prevention of cervical cancer caused by HPV types 16 and 18. Gardasil® 9 (HPV9 vaccine) was authorized with a 3-dose schedule for use in Canada on February 5, 2015 for the prevention of infection caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58, and for prevention of anogenital cancers, related pre-cancerous lesions, and AGWs associated with the HPV types included in the vaccine. The HPV9 vaccine was recommended for use by NACI in July, 2016.

An ongoing phase III study has recently yielded data demonstrating that HPV9 vaccine immunogenicity following a 2-dose immunization schedule was not inferior to a 3-dose schedule in both females and males. The safety profile of a 2-dose schedule was also similar to that of a 3-dose schedule. Gardasil®9 was authorised for use in Canada according to a 2-dose immunization schedule on December 15, 2016.

Several recent studies have also examined the safety and immunogenicity of HPV2 and HPV4 vaccines in immunocompromised populations.

2. Who

Girls and Women

HPV2, HPV4, and HPV9 vaccines are indicated in all females aged 9 to 45 years. HPV2 vaccine is indicated in females 9 to 45 years of age for the prevention of cervical cancer and pre-cancerous lesions associated with the HPV types contained in the vaccine. HPV4 and HPV9 vaccines are indicated for the prevention of the following diseases associated with the HPV types contained in the vaccines:

In females 9 to 45 years of age

- Cervical, vulvar, vaginal cancers and pre-cancerous lesions
- AGWs

In females 9 to 26 years of age

- Anal cancer and pre-cancerous lesions

Boys and Men

HPV4 and HPV9 vaccines are indicated in all males 9 to 26 years of age for the prevention of anal cancers, pre-cancerous lesions and AGWs. HPV2 vaccine is not indicated in males at this time.

HPV vaccines are **not** indicated in:

- females or males < 9 years of age as no immunogenicity or efficacy data are available in these groups

3. How

HPV vaccines have been authorized by the Canadian federal regulator, Health Canada, to be given as **three** separate 0.5 mL doses:

- HPV2 vaccine at months 0, 1, and 6,
- HPV4 vaccine at months 0, 2, and 6, and
- HPV9 vaccine at months 0, 2 and 6.

HPV vaccines have also been authorized by the Canadian federal regulator, Health Canada, to be given in **two** separate 0.5 mL doses in younger immunocompetent individuals:

- HPV2 vaccine at months 0 and 6 in girls aged 9 to 14 years of age at the time of first injection (authorization on July 3, 2014)
- HPV4 vaccine at months 0 and 6 or 0 and 12 in individuals 9 to 13 years of age (authorization on March 10, 2015)
- HPV9 vaccine at months 0 and 5-13 in individuals 9 to 14 years of age (authorization on December 15, 2016)

Based on current evidence, NACI recommends that (see Table 1 for a summary of these recommendations, and the grade of evidence on which these recommendations are based):

- Either a 2 or 3-dose immunization schedule with HPV9 vaccine can be used for immunocompetent females and males 9-14 years of age (as with HPV2 or HPV4 vaccines). In a 2-dose schedule, the second dose should be administered at least 24 weeks after the first dose;
- HPV9 vaccine can be administered according to a 3-dose immunization schedule in males or females ≥15 years (as with HPV2 or HPV4 vaccines);
- A 3-dose schedule should be maintained for HPV2, HPV4, or HPV9 vaccines in immunocompromised populations, immunocompetent HIV infected individuals, and individuals who have not received any dose of HPV vaccine by 15 years of age, ensuring at least 24 weeks between the first and last dose of HPV vaccine.

Table 1. NACI Recommendations for the HPV Immunization Schedule

RECOMMENDED GROUPS	RECOMMENDED IMMUNIZATION SCHEDULE	HPV VACCINES AND NACI EVIDENCE GRADE (see Table 8 for an explanation of NACI's grading of evidence)
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)	2- or 3-dose schedule	HPV2 or HPV4 (Grade A); HPV9 (Grade B)
Healthy (immunocompetent, non-HIV infected) Females ≥15 years of age	3-dose schedule	HPV2 or HPV4 (Grade A) or HPV9 (Grade 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)	2- or 3-dose schedule	HPV4 or HPV9 (Grade B)
Healthy (immunocompetent, non-HIV infected) Males ≥15 years of age	3-dose schedule	HPV4 or HPV9 (Grade B)
Immunocompromised individuals and immunocompetent HIV-infected individuals	3-dose schedule	HPV2 or HPV4 in females (Grade B); HPV4 in males (Grade B); HPV9 in females or males (Grade I)

Efforts should be made to administer HPV vaccines at the recommended intervals. When an abbreviated schedule is required, vaccine doses should not be administered earlier than the minimum intervals between doses. In a 3-dose schedule, the minimum interval between the first and second doses of vaccine is 4 weeks, the minimum interval between the second and third doses of vaccine is 12 weeks and **the minimum interval between the first and last doses in either a 2-dose or 3-dose schedule is 24 weeks.**

There is insufficient evidence at this time to recommend, at a population level, re-immunization with HPV9 vaccine in individuals who have completed an immunization series with another HPV vaccine, as discussed in the previous Statement[(1)].

Because fainting post-vaccination is more common in younger people, it is particularly important to observe each vaccinee for 15 minutes after vaccine administration to avoid serious injury in the event of syncope.

4. Why

In the absence of vaccination, it is estimated that 75 per cent of sexually active Canadians will have a sexually transmitted HPV infection at some point in their lives. Even if a person is already infected with one or more vaccine HPV type(s), the vaccine will provide protection against the other HPV type(s) contained in the vaccine. Immunocompromised individuals are at increased risk for HPV infection and associated cancers.

In Canada, immunization against HPV types 16 and 18 with HPV2, HPV4 or HPV9 vaccine can prevent approximately 70% of anogenital cancers and 60% of high-risk precancerous cervical lesions. Immunization with HPV9 can prevent up to an additional 14% of anogenital cancers and up to 30% of high-risk precancerous cervical lesions caused by the additional five HPV types (31, 33, 45, 52 and 58) against which the vaccine protects. Immunization with either HPV4 or HPV9 can prevent approximately 85-90% of AGWs (HPV types 6 and 11).

A 2-dose immunization schedule for HPV9 vaccine may be preferred by some jurisdictions based on consistency with existing HPV4 vaccine programs, as well as other individual and programmatic advantages.

I. INTRODUCTION

In April, 2016, a NACI Statement was released as an advance copy to provincial and territorial stakeholders to summarise the evidence and recommendations regarding the nine-valent human papillomavirus vaccine (HPV9) (Gardasil®9, Merck Canada, Inc.) authorized for use in Canada on February 2015, and to clarify minimum intervals between doses of HPV vaccines for 2-dose and 3-dose schedules[1]. The Statement was published online in July, 2016. When the previous Statement was written, there was insufficient evidence for NACI to recommend a 2-dose immunization schedule with HPV9 vaccine. However, new data have emerged evaluating a 2-dose immunization schedule for HPV9 vaccine in males and females. NACI has reviewed this newly acquired evidence to provide timely guidance on the possibility of a 2-dose immunization schedule for HPV9 vaccine. HPV9 vaccine was authorized for use in Canada according to a 2-dose immunization schedule on December 15, 2016.[2]

Previous NACI statements have also discussed the use of HPV vaccines in immunocompromised populations, but this discussion has been largely in the absence of strong evidence for these groups. Recently, a growing number of studies have specifically explored the responses of immunocompromised subgroups to HPV vaccines, which has triggered a NACI Literature Review on this topic.

This statement will:

- Review evidence for a 2-dose immunization schedule of the HPV9 vaccine, and provide recommendations;
- Summarise evidence from a recent NACI Literature Review on the use of HPV vaccines in immunocompromised populations, and provide recommendations for HPV vaccine use in these groups.

II. METHODS

HPV9 vaccine, 2-dose schedule

NACI reviewed key questions on HPV9 vaccine as proposed by the HPV Working Group (HPV WG), including: the safety, immunogenicity, and efficacy of the HPV9 vaccine with a 2-dose immunization schedule[1]. The knowledge synthesis, including an environmental scan, was performed by a PHAC Scientific Project Co-ordinator, PHAC Medical Specialist, and the HPV WG. Only one clinical trial was identified, the results of which have not been previously peer-reviewed but were presented to the HPV WG on November 26, 2015, followed by a presentation to NACI on February 10, 2016, then presented publicly on February 24, 2016, at an Advisory Committee on Immunization Practices (ACIP) meeting[3]. Abridged methods and results for this study (V503-010) are available at the international clinical trials registry and results database ClinicalTrials.gov[4]. NACI sought and acquired additional unpublished methodological information from the clinical trial lead (in this case the vaccine manufacturer, Merck) to evaluate the methodology according to NACI's established criteria. The NACI HPV WG reviewed the study methods and results, and two independent reviewers appraised the study for internal validity to assign the level and quality of evidence, which was validated by the Working Group Chair. While this evidence has yet to be formally published in a peer-reviewed journal, at the time of writing this statement, a modified peer-review process of the study was conducted by the Working Group and NACI. This evidence was included for knowledge

synthesis based on its scientific merits. On April 4, 2016, the European Medicines Agency was the first regulatory body to authorise the use of Gardasil®9 vaccine according to a 2-dose schedule, based on a review of the data submitted from study V503-010[5]. Moreover, the United Kingdom (UK) Joint Committee on Vaccination and Immunisation reviewed immunogenicity and safety data at their meeting on June 1, 2016, concluding that HPV9 vaccine can be used with a 2-dose immunization schedule in the UK female program[6]. Gardasil®9 was authorized for use in Canada according to a 2-dose immunization schedule on December 15, 2016.[2]

Following critical appraisal of the study V503-010, a summary table was prepared with ratings of the evidence quality using NACI's methodological hierarchy (Table 6), and proposed recommendations were developed. The evidence and proposed recommendations were presented to NACI`s HPV WG on February 10, and May 16, 2016. The committee adopted specific recommendations following thorough review of the evidence at the NACI meeting on June 9, 2016, and a final review on August 29, 2016.

HPV vaccines in immunocompromised populations

NACI reviewed key questions for a literature review on HPV vaccines as proposed by the HPV Working Group, including the specific question: “Do immunization outcomes differ for subgroups of immunocompromised populations?” A literature review was conducted according to established NACI methodology[7]. Details of this literature review and associated methodology (search terms, inclusion/exclusion criteria, databases, number of results) can be found in the *NACI Literature Review for HPV Immunization of Immunocompromised Populations*. The knowledge synthesis, including an environmental scan and literature review, was performed by a PHAC Scientific Project Co-ordinator and then reviewed by a PHAC Medical Specialist and the HPV Working Group. Following critical appraisal of individual studies, summary tables were prepared with ratings of the evidence quality using NACI's methodological hierarchy (Table 6), and proposed recommendations were developed. The evidence and proposed recommendations were presented to the NACI HPV WG on February 10, 2016. Following thorough review of the evidence at the NACI meeting on June 9, 2016, and a final review on August 29, 2016, the committee adopted specific recommendations.

III. EPIDEMIOLOGY

There is strong epidemiological evidence that persistent infection with high-risk HPV types can lead to the development of pre-cancerous lesions that can progress to cancers of the cervix, vulva, and vagina in females, penile cancer in males, and anal and oropharyngeal cancer in both females and males[8-10]. Besides the members of the HPV alpha-7 species (HPV types 18 and 45) that are over-represented in glandular lesions, other high-risk HPV types are primarily associated with epithelial, squamous cell carcinomas.

A full review of HPV type epidemiology for either immunocompetent or immunocompromised populations was not conducted as it was not an objective of this Advisory Committee Statement.

HPV9 vaccine types

A complete assessment of estimated burden of disease for the HPV types contained in the HPV2, HPV4, and HPV9 vaccines can be found in the previous NACI Statement titled “Updated Recommendations on Human Papillomavirus (HPV) Vaccines: 9-valent HPV vaccine and clarification of minimum intervals between doses in the HPV immunization schedule”[1].

Immunocompromised populations

Accumulating evidence suggests the rates of HPV infection and associated disease are increased in immunocompromised populations including both HIV-infected populations[11] and solid organ transplant recipients[12]. A meta-analysis found that standardised incidence ratios for HPV-related cancers in these immunocompromised groups ranged from 1.6 to 30 times greater than the general population[13].

IV. HPV9 VACCINE

IV.1 Preparations of HPV vaccines authorized for use in Canada

Characteristics of the HPV vaccines currently authorized for use in Canada are summarized in Table 2.

Table 2. Comparison of HPV Vaccines Authorized for Use in Canada

Product Details	Cervarix® (HPV2)	Gardasil® (HPV4)	Gardasil 9® (HPV9)
Immunogens ***(Recombinant L1 proteins from HPV types:)***	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
Manufacturer	GlaxoSmithKline Inc.	Merck Canada Inc.	Merck Canada Inc.
Authorization	• females 9-45 years	• females 9-45 years • males 9-26 years	• females 9-45 years • males 9-26 years
Antigen Components (µg):			
HPV type 18 L1 protein	20	20	40
HPV type 16 L1 protein	20	40	60
HPV type 11 L1 protein		40	40
HPV type 6 L1 protein		20	30
HPV type 31 L1 protein			20
HPV type 33 L1 protein			20
HPV type 45 L1 protein			20
HPV type 52 L1 protein			20
HPV type 58 L1 protein			20
Adjuvant	500 µg aluminum hydroxide 50 µg 3-O-desacyl-4'-monophosphoryl lipid A (AS04)	225 µg amorphous aluminum hydroxyphosphate sulphate (AAHS)	500 µg amorphous aluminum hydroxyphosphate sulphate (AAHS)
Other ingredients	sodium chloride, sodium dihydrogen phosphate dihydrate, water for injection	sodium chloride, L-histidine, polysorbate 80, sodium borate, water for injection	L-histidine, polysorbate 80, sodium borate, sodium chloride, and water for injection

IV.2 Efficacy of HPV9 Vaccine 2-dose schedule

HPV vaccines have been authorized for use based on the demonstration of their clinical efficacy in females, 16 to 45 years of age, and males, 16 to 26 years of age. In younger individuals, efficacy has been inferred using pre-licensure immunogenicity bridging studies that have demonstrated non-inferiority in antibody responses to antigens in the vaccine among different age groups. The underlying premise of immuno-bridging studies is that if the trial population attains similar antibody levels as the population in which efficacy is already established, efficacy results can be inferred in the trial population. There is currently no known immunological correlate for protection from HPV infection.

For a 2-dose immunization schedule of HPV9 vaccine (0,6 months or 0,12 months), immunogenicity analyses demonstrate non-inferiority for young females (9-14 years) compared to adult female (16-26 years) recipients of 3-doses, for whom HPV9 vaccine efficacy has been previously demonstrated for infection and disease related to HPV types 31, 33, 45, 52, and 58[1, 14]. Immunogenicity analyses following a 2-dose vaccine schedule for HPV9 in young females also demonstrate non-inferiority for HPV types 6, 11, 16, and 18, compared to adult female (16-26 years) who received 3 doses of HPV9 vaccine, which were in turn non-inferior to adult female responses using a 3-dose immunization schedule of HPV4 vaccine, for whom efficacy has been previously established for infection and disease related to HPV types 6, 11, 16, and 18[14].

The efficacy of a 2-dose immunization schedule for the HPV9 vaccine can therefore be inferred based on the principle of immuno-bridging from the available data.

IV.3 Immunogenicity of HPV9 vaccine 2-dose schedule

An ongoing phase III RCT (Merck protocol V503-010) examined the immunogenicity and safety of a 3-dose versus a 2-dose immunization schedule for HPV9 vaccine[3, 4]. While there is currently no known correlate for HPV protection following immunization, seroconversion rates and anti-HPV IgG GMTs are often used across groups to compare relative immunity; these immunogenicity data can later be used to interpret efficacy based on the principle of immuno-bridging.

This study is currently the only evidence that directly examines immunogenicity outcomes for a 2-dose immunization schedule with HPV9 vaccine, and was rated as level I evidence of good quality by two independent reviewers and the Working Group Chair; this rating was supported by the Working Group and NACI. The study enrolled 753 girls, 9-14 years of age, 451 boys, 9-14 years of age, and 314 young women, 16-26 years of age, into 6 treatment groups. The primary objective was to compare 2 doses (0, 6 months) of HPV9 vaccine in girls and boys (9-14 years) to women receiving 3 doses (0, 2, 6 months) of HPV9 vaccine. 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. However, a recent study from India[15] has suggested that 2 doses of HPV4 vaccine may be immunogenic in females aged 10-18 years, and NACI will continue to review similar evidence as it emerges to identify the optimal HPV9 immunization schedule for persons 15 years of age and older.

Females: 2-dose immunization schedule (0, 6 months)

Data suggest that the immunogenicity of a 2-dose HPV9 vaccine schedule in girls was comparable to the immunogenicity of a 3-dose immunization schedule in women.

The GMT antibody results of 290 girls aged 9-14 who received 2 doses of HVP9 vaccine (0,6 months) were measured 1 month following the last dose of vaccine and compared to results from 308 women aged 16-26 who received 3 doses of the same vaccine (0,2,6 months). GMTs against all 9 HPV vaccine types were non-inferior in girls who received 2 doses (0,6 months) of HPV9 vaccine compared to women who received 3 doses (0,2,6 months) of HPV9 vaccine, with GMT ratios ranging from 1.60 to 2.96 fold higher than the responses from 3-dose recipients.

Seroconversion rates exceeded 99% against all 9 HPV vaccine types in the girls aged 9-14, one month following the last dose of vaccine in a 2-dose (0,6 months) schedule. Similarly, seroconversion rates for women on a 3-dose (0,2,6 months) immunization schedule exceeded 99% for 8 of 9 HPV vaccine types, with 97.9% seroconversion for HPV 45.

Females: alternate 2-dose immunization schedule (0,12 months)

To explore an extended dose interval, a combined group of 145 girls and 147 boys received 2 doses of HPV9 vaccine at 0 and 12 months. Seroconversion rates for this combined group were 100% for all 9 HPV vaccine types. The GMTs against all 9 HPV vaccine types in this group of boys and girls were non-inferior, compared to the women who received 3 doses (0,2,6 months) of HPV9 vaccine.

Although the two 2-dose immunization schedules (0,6 months versus 0,12 months) were not directly compared statistically on the basis of immunogenicity, it can be observed that the GMT ratios in boys and girls receiving a longer 2-dose interval (0,12 months) ranged from 1.96 to 6.31 fold higher than the responses from women on a 3-dose schedule (0,2,6 months) for all 9 HPV vaccine types, with most ratios exceeding 3. By contrast, GMT ratios for boys and girls receiving a shorter 2-dose interval (0,6 months) ranged from 1.65 to 2.99 fold higher than the responses from women on a 3-dose schedule (0,2,6 months). These findings suggest that a 0,12 month schedule may have advantages from an immunogenicity perspective compared to a 0, 6 month schedule. The clinical significance of this finding is unknown. Although long-term follow-up data are not currently available for a 2-dose schedule with HPV9, a study is currently underway to evaluate the duration of vaccine responses up to 36 months.

An exploratory analysis was performed to compare GMTs at 1 month following the last dose of vaccine in girls aged 9-14 who received a 2-dose schedule (0,6 months or 0,12 months) versus a 3-dose schedule (0,2,6 months) in the same age group. Lower GMTs were observed for HPV types 18, 31, 45, and 52 in girls who received 2 doses of HPV9 vaccine (0,6 months), compared to girls of the same age who received 3 doses of HPV9 vaccine (0,2,6 months). GMT ratios ranged from 0.54 to 1.29 fold compared to responses in 3-dose recipients. Notably, in girls receiving an alternative 2-dose immunization schedule (0,12 months), only the GMT for HPV type 45 was lower compared to girls receiving a 3-dose HPV9 immunization schedule (0,2,6 months), with a GMT ratio of 0.66. The clinical significance of these exploratory comparisons is unknown and there are currently no long-term follow up or efficacy data available for either 2-dose immunization schedule with HPV9 vaccine in females (0,6 months or 0, 12 months) or a 3-dose immunization schedule (0,2,6 months). However, both of these 2-dose immunization schedules in girls (aged 9-14) were non-inferior when compared to women (aged 16-26) with a 3-dose schedule (0,2,6 months) for which immuno-bridging efficacy data are available.

Males: 2-dose immunization schedule (0,6 months)

Data suggest that the immunogenicity of a 2-dose HPV9 vaccine schedule in boys was comparable to the immunogenicity of a 3-dose immunization schedule in women.

The GMT antibody results of 294 boys aged 9-14 who received 2 doses of HVP9 vaccine (0,6 months) were also compared to results from 308 young women aged 16-26 who received 3 doses of the same vaccine (0,2,6 months). GMTs against all 9 HPV vaccine types were non-inferior in boys who received 2 doses (0,6 months) of HPV9 vaccine compared to women who received 3 doses (0,2,6 months) of HPV9 vaccine, with GMT ratios ranging from 1.65 to 2.99 fold higher than the responses from 3-dose recipients. Seroconversion rates exceeded 99% against all 9 HPV vaccine types in these boys aged 9-14 at 1 month following the last dose of vaccine in a 2-dose (0,6 months) schedule.

To explore an extended dose interval, a combined group of 145 girls and 147 boys received 2 doses of HPV9 vaccine at 0 and 12 months. Seroconversion rates in this combined group were 100% for all 9 HPV vaccine types. The GMTs against all 9 HPV vaccine types in this group of boys and girls were non-inferior, compared to the women who received 3 doses (0,2,6 months) of HPV9 vaccine, with GMT ratios ranging from 1.96 to 6.31 fold higher than the responses from 3-dose recipients.

Males: alternate 2-dose immunization schedule (0,12 months)

Although the two 2-dose immunization schedules (0,6 months versus 0,12 months) were not directly compared statistically on the basis of immunogenicity, it can be observed that the GMT ratios in boys and girls receiving a longer 2-dose interval (0,12 months) ranged from 1.96 to 6.31 fold higher than the responses from women on a 3-dose schedule (0,2,6 months) for all 9 HPV vaccine types, with most ratios exceeding 3. By contrast, GMT ratios for boys and girls receiving a shorter 2-dose interval (0,6 months) ranged from 1.65 to 2.99 fold higher than the responses from women on a 3-dose schedule (0,2,6 months). These findings suggest that a 0,12 month schedule may have advantages from an immunogenicity perspective compared to a 0, 6 month schedule. The clinical significance of this is unknown. Although long-term follow-up data are not currently available for a 2-dose schedule with HPV9, a study is currently underway to evaluate the duration of vaccine responses up to 36 months.

Table 3. Summary of GMTs by HPV type according to immunization schedule, 1 month following last dose - mMU/mL (95%CI) determined by cLIA

HPV type	**0,6** months Girls	**0,6** months Boys	**0,12** months Girls/ boys	**0,2,6** months Girls	**0,2,6** months Women
6	**1657.9** (1479.6 - 1857.6)	**1557.4** (1391.5 - 1743.1)	**2678.8** (2390.2 - 3002.1)	**1496.1** (1334.1 - 1677.8)	**770.9** (684.8 - 867.9)
11	**1388.9** (1240.4 - 1555.3)	**1423.9** (1273.2 - 1592.3)	**2941.8** (2626.6 - 3294.9)	**1306.3** (1165.5 - 1464.0)	**580.5** (516.0 - 653.0)
16	**8004.9** (7160.5 - 8948.8)	**8474.8** (7582.4 - 9472.3)	**14329.3** (12796.4 - 16045.9)	**6996.0** (6254.1 - 7825.8)	**3154.0** (2807.1 - 3543.7)
18	**1872.8** (1651.6 - 2123.6)	**1860.9** (1641.1 - 2110.2)	**2810.4** (2474.9 - 3191.3)	**2049.3** (1806.4 - 2324.8)	**761.5** (670.8 - 864.5)
31	**1436.3** (1272.1 - 1621.8)	**1498.2** (1326.5 - 1692.0)	**2117.5** (1873.7 - 2393.1)	**1748.3** (1548.1 - 1974.5)	**572.1** (505.8 - 647.2)
33	**1030.0** (920.4 - 1152.7)	**1040.0** (928.9 - 1164.3)	**2197.5** (1961.9 - 2461.3)	**796.4** (712.0 - 890.9)	**348.1** (311.5 - 389.1)
45	**357.6** (313.7 - 407.6)	**352.3** (309.0 - 401.7)	**417.7** (365.9 - 476.9)	**661.7** (580.6 - 754.1)	**213.6** (187.7 - 243.2)
52	**581.1** (521.9 - 647.1)	**640.4** (575.2 - 713.0)	**1123.4** (1008.1 - 1251.9)	**909.9** (817.6 - 1012.5)	**364.2** (327.0 - 405.6)
58	**1251.2** (1119.6 - 1398.4)	**1325.7** (1186.2 - 1481.6)	**2444.6** (2185.2 - 2734.9)	**1229.3** (1100.7 - 1373.0)	**491.1** (438.6 to 549.8)

Table 4. Summary of seroconversion rates by HPV type according to immunization schedule, 1 month following last dose - % (95%CI) determined by cLIA

HPV type	**0,6** months Girls	**0,6** months Boys	**0,12** months Girls/ boys	**0,2,6** months Girls	**0,2,6** months Women
6	**99.6** (97.9 - 100)	**100** (98.6 - 100)	**100** (98.6 - 100)	**99.2** (97.2 - 99.9)	**99.6** (97.7 - 100)
11	**100** (98.6 - 100)	**100** (98.6 - 100)	**100** (98.6 - 100)	**99.6** (97.8 - 100)	**99.6** (97.7 - 100)
16	**100** (98.7 - 100)	**100** (98.7 - 100)	**100** (98.6 - 100)	**100** (98.6 - 100)	**99.6** (97.8 - 100)
18	**100** (98.7 - 100)	**100** (98.7 to 100)	**100** (98.6 - 100)	**99.6** (98.0 - 100)	**98.5** (96.2 - 99.6)
31	**99.6** (98.0 - 100)	**100** (98.6 - 100)	**100** (98.6 - 100)	**100** (98.6 - 100)	**99.6** (97.9 - 100)
33	**99.6** (98.0 - 100)	**100** (98.6 - 100)	**100** (98.6 - 100)	**100** (98.7 - 100)	**99.6** (98.0 - 100)
45	**99.3** (97.4 - 99.9)	**99.3** (97.4 - 99.9)	**100** (98.6 - 100)	**99.3** (97.4 - 99.9)	**97.9** (95.4 - 99.2)
52	**99.6** (98.0 - 100)	**100** (98.7 - 100)	**100** (98.6 - 100)	**99.6** (98.0 - 100)	**99.6** (98.0 - 100)
58	**100** (98.6 - 100)	**100** (98.6 - 100)	**100** (98.6 - 100)	**99.6** (98.0 - 100)	**99.6** (97.9 - 100)

IV.4 Safety of HPV9 vaccine 2-dose schedule

The HPV9 vaccine was safe and well-tolerated with either a 2-dose or 3-dose schedule. No deaths occurred, nor were any expected, in any of the vaccine recipients. Serious adverse events (SAEs) were recorded in 23 out of 1496 subjects, but none were deemed to be related to the vaccine.

Females

No vaccine-related SAEs or AEs resulting in discontinuation of vaccination were observed in the 294 girls (aged 9-14) randomized to a 2-dose immunization schedule (0,6 months) with follow-up. Similarly, no vaccine-related SAEs or AEs resulting in discontinuation of vaccination were observed in the 300 girls (aged 9-14) or 313 women (aged 16-26) randomized or allocated to a 3-dose immunization schedule (0,2,6 months) with follow-up.

Males

No vaccine-related SAEs or AEs resulting in discontinuation of vaccination were observed in the 296 boys (aged 9-14) randomized to a 2-dose immunization schedule (0,6 months) with follow-up. Among the combined 293 girls and boys receiving 2 doses of HPV9 vaccine (0,12 months) with follow up there were no vaccine-related SAEs and one AE of urticaria that resulted in a discontinuation of the schedule for the affected subject.

IV.5 Vaccine Administration and Schedule

Vaccine Administration

HPV9 vaccine is administered by intra-muscular injection. Gardasil® 9 is authorized for use in Canada by the Canadian federal regulator, Health Canada, as a 3-dose schedule at 0, 2, and 6 months; or as a 2-dose schedule at 0 and 5-13 months. Based on the NACI modified peer review of recent clinical trial data presented by Merck, 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 is the case with HPV2 or HPV4 vaccines in this population. The second dose of HPV9 vaccine in a 2-dose schedule should not be administered earlier than 24 weeks (6 months) following the first dose.

V. HPV VACCINES IN IMMUNOCOMPROMISED POPULATIONS

A detailed literature review of HPV immunization outcomes in immunocompromised populations was conducted by PHAC and was used by NACI for the recommendations in this Statement. Key evidence from the literature review is summarized below, and the complete literature review can be found online. The complete list of studies is included in the evidence table of NACI's Literature Review on this topic.

V.1 Evidence for Immunogenicity in HIV-infected Populations

Of 10 relevant studies identified, only 1 was rated as good quality, while 8 were rated as fair, and the quality of 1 abstract could not be rated due to limited information. Overall, the majority of HIV-infected subjects in identified studies had CD4 counts ≥350 cells/μL, uninfected controls were generally not available for comparison, and historical controls were often used. Seroconversion rates and titre responses in these subjects were typically high, but some evidence showed that anti-HPV titre levels trended lower than in uninfected historical controls, although the antibody responses still typically exceed those resulting from natural infection in immunocompetent individuals. Adding a fourth vaccine dose appeared to improve titre responses and seroconversion rates in one study.

Among HIV-infected subjects with low CD4 levels (≤200 cells/μL), seroconversion rates were significantly lower than in infected subjects with higher CD4 levels; titres were also numerically less than in the comparator group, but only the titre for HPV6 was significantly lower. Similarly, an HIV RNA load >10 000 copies/mL was significantly associated with low seroconversion rates, while an RNA load >5000 was significantly associated with low anti-HPV titre responses.

In studies of HIV-infected subjects with varied CD4 levels, HPV vaccination produced good seroconversion rates but anti-HPV titres in HIV-infected groups trended lower than uninfected controls. The viral load or anti-retroviral therapy status of subjects and the vaccine type used may be factors. One study also reported that HIV-infected females immunized with the bivalent vaccine Cervarix® had significantly higher GMTs than those immunized with quadrivalent Gardasil®. See the NACI Literature Review on this topic for complete details and analyses of the individual studies.

V.2 Evidence for Immunogenicity in Acquired Therapeutic Immunodeficiency

Of 11 relevant studies identified, only 3 were rated as good quality while 4 were rated as fair, 2 were rated as poor quality, and the quality of 2 abstracts could not be rated due to limited information. Overall, patients receiving therapeutic immunosuppression for transplant or who suffer from autoimmune or inflammatory disorders often respond to HPV vaccination, but seroconversion rates and titre responses can be significantly lower than in healthy controls. However, antibody responses still typically exceed those resulting from natural infection in immunocompetent individuals. Some evidence suggests that certain treatment modalities have a greater impact than others, but there is insufficient evidence to identify specifically the treatments that are more likely to result in lower titres in the context of HPV immunization. See the NACI Literature Review on this topic for complete details and analyses of the individual studies.

V.4 Evidence for Safety in HIV-infected Populations

Of 9 relevant studies identified, 3 were rated as good quality, 5 were rated as fair, and 1 abstract could not be rated. Overall, HPV vaccination of HIV-infected patients was safe and well-tolerated. Furthermore, HPV immunization did not affect CD4 levels or HIV viral load in any study. Unfortunately, most studies did not include uninfected immunized controls, or HIV-infected unimmunized controls, for comparison. Some studies suggest that local reactions were more common in HIV-infected subjects than uninfected controls, and one study, rated as good,

suggests that local reactions were more common with Cervarix® than with Gardasil®. SAEs were uncommon, and only 1 SAE was considered possibly associated with immunization. See the NACI Literature Review on this topic for complete details and analyses of the individual studies.

V.5 Evidence for Safety in Acquired Therapeutic Immunodeficiency

Of 13 relevant publications identified, 3 were case reports. Only 4 studies were rated as good quality while 3 were rated as fair, 5 were rated as poor quality, and the quality of 1 abstract could not be rated due to limited information. Overall, HPV vaccination of patients receiving therapeutic immunosuppression for transplant or autoimmune or inflammatory disorders was safe and well-tolerated. Incomplete datasets and a general lack of control groups make direct safety comparisons difficult. Four publications contain 9 case reports on the flare or new onset of autoimmune disease following HPV immunization; however larger cohort studies indicate that these diseases are not adversely affected by HPV immunization. See the NACI Literature Review on this topic for complete details and analyses of the individual studies.

VI. RECOMMENDATIONS

Since February 5, 2015, there have been three HPV vaccines authorized for use in Canada. All of these vaccines are authorized for use with either a 3- dose or a 2-dose immunization schedule

HPV2, HPV4, and HPV9 vaccines all protect against HPV types 16 and 18, which are responsible for approximately 70% of anogenital cancers. HPV9 protects against 5 additional HPV genotypes estimated to be responsible for approximately 14% of anogenital cancers in females and 4% in males in the United States of America[16]. HPV4 and HPV9 also protect against HPV genotypes 6 and 11, which cause 85-90% of AGWs[17, 18]. At the population level, if all persons recommended for the vaccine receive it, and there is one hundred percent long-term efficacy, immunization with HPV9 vaccine in Canada can potentially prevent annually up to 320 additional cases of anogenital cancers (300 in females and 20 in males).

Adverse events following immunization with HPV vaccines primarily include mild to moderate injection site-related pain, erythema and swelling. These local adverse events are more common in HPV9 vaccine recipients compared to recipients of the HPV4 vaccine.

NACI schedule recommendations regarding HPV2 and HPV4 vaccines, as summarized in the Introduction of this statement, are still applicable. Please refer to the 2012 NACI Statement Update on HPV Vaccines (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/12vol38/acs-dcc-1/index-eng.php), the 2015 NACI Update on the Recommended HPV vaccine immunization schedule (http://www.phac-aspc.gc.ca/naci-ccni/acs-dcc/2015/hpv-vph_0215-eng.php), and the 2016 NACI Update on recommended minimum intervals and the 9-valent HPV vaccine (http://www.healthycanadians.gc.ca/publications/healthy-living-vie-saine/human-papillomavirus-9-valent-vaccine-update-recommendation-mises-a-jour-recommandations-papillome-humain-vaccin-nonavalent/index-eng.php) for a complete list of these recommendations. New recommendations regarding a 2-dose immunization schedule for HPV9 vaccine and the use of HPV vaccines in immunocompromised populations are summarized below.

The new and complete set of current recommendations for HPV vaccines will be published in the updated HPV chapter in the Canadian Immunization Guide (http://www.phac-aspc.gc.ca/publicat/ciggci/p04-hpv-vph-eng.php) in the near future.

Please note that provinces and territories must consider economic factors and other local programmatic and operational factors when considering inclusion of the following recommendations in publicly funded immunization programs.

Please refer to Table 8 for an explanation of NACI grading of evidence.

I. RECOMMENDATIONS FOR 2-DOSE HPV9 SCHEDULE IN IMMUNOCOMPETENT POPULATIONS

Recommendation #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)

NACI concludes that there is now fair evidence to recommend a 2-dose immunization schedule with HPV9 vaccine, although evidence is limited in quantity. Therefore, based on the current evidence reviewed for this and previous Advisory Committee Statements, NACI concludes that there is fair evidence to recommend either a 2-dose or a 3-dose immunization schedule with HPV9 vaccine (Evidence Grade B) and that there is good evidence to recommend either a 2-dose or a 3 dose immunization schedule with HPV2 or HPV4 vaccines in females and HPV4 vaccine in males. In a 2-dose HPV immunization schedule with any HPV vaccine authorized for use in Canada, the second dose should not be administered earlier than 24 weeks (6 months) following the first dose. Although long-term follow-up data are not currently available for a 2-dose schedule with HPV9, a study is currently underway to evaluate the duration of vaccine responses up to 36 months. As further evidence becomes available, the grade of this recommendation may change. There is no evidence to suggest that individuals will respond differently to HPV9 vaccine compared to either HPV2 or HPV4 vaccines.

Recommendation #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. This recommendation is outlined in the previous statement titled “Updated Recommendations on Human Papillomavirus (HPV) Vaccines: 9-valent HPV vaccine and clarification of minimum intervals between doses in the HPV immunization schedule”. However, a recent study in India has suggested that 2 doses of HPV4 vaccine may be immunogenic in females aged 10-18 years, and NACI will continue to review similar evidence as it emerges to identify the optimal HPV9 immunization schedule for persons 15 years of age and older.

II. RECOMMENDATIONS FOR HPV VACCINATION IN PERSONS WHO ARE IMMUNOCOMPROMISED AS A RESULT OF DISEASE OR MEDICATIONS

Recommendation #3

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)

While NACI's recommendation regarding HPV2 and HPV4 vaccines in this population remains unchanged, based on the Literature Review conducted to inform these recommendations the Evidence Grade on which the recommendation is based has been upgraded from a Grade I (insufficient evidence in either quantity and/or quality to make a recommendation, however other factors may influence decision-making) to a Grade B (fair evidence to make a recommendation). Evidence does not suggest there are any unique safety concerns in using HPV2 or HPV4 vaccines for immunocompromised populations. There are currently no studies directly evaluating the immunogenicity, efficacy, or safety of HPV9 vaccine in immunocompromised populations with either a 3-dose or a 2-dose schedule; therefore the Evidence Grade on which the recommendation is based is Grade I. However, there is no evidence to suggest that individuals would respond differently to HPV9 vaccine compared to either HPV2 or HPV4 vaccines. As further evidence becomes available, the grade of this recommendation may change.

There are currently no published studies exploring a 2-dose HPV immunization schedule in immunocompromised populations. NACI concludes that there is fair evidence demonstrating that the immunogenicity of HPV2 and HPV4 vaccines can be diminished in immunocompromised populations following a 3-dose immunization schedule, although the antibody responses still typically exceed those resulting from natural infection in immunocompetent individuals. Therefore, although the immunogenicity and efficacy have not been fully characterised in all immunocompromised populations, individuals who are immunocompromised 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.

Table 1 summarizes these recommendations. HPV immunization may be completed with HPV2, HPV4 or HPV9 vaccines in females and HPV4 or HPV9 vaccines in males, according to the immunization schedules summarized in this table. Where possible, the same 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 HPV9 vaccine among immunocompetent 9-26 year olds is expected to provide similar protective efficacy against genotypes contained in the HPV4 vaccine. Moreover, HPV9 vaccine protects against the additional five HPV types not contained in HPV4 vaccine (HPV 31, 33, 45, 52 and 58).

VII. RESEARCH PRIORITIES

Research priorities and outstanding research questions have previously been identified through the 2005 HPV Research Priorities Workshop, as well in the 2012 and 2015 NACI HPV Advisory Committee Statements. HPV immunization experts met in June 2013, added to the list of research priorities previously documented, and also encouraged a more co-ordinated and collaborative approach between jurisdictions to reduce duplication of research efforts. A complete list of research priorities previously identified is accessible in the Canadian Immunization Committee's Recommendations for Human papillomavirus Immunization Programs document. (http://publications.gc.ca/site/eng/464264/publication.html)

Priority research questions to address outstanding issues specifically related to the current NACI statement include the following:

1. Determination of immune correlates for protection against HPV infection.
2. Evaluation of long-term immunogenicity kinetics and outcomes for a 2-dose versus 3-dose HPV9 vaccine immunization schedule.
3. Direct comparison between alternative 2-dose immunization schedules for HPV9 vaccine (0,6 months versus 0,12 months).
4. Evaluation of 9-valent HPV vaccine in immunocompromised populations.
5. Follow up of vaccinated immunocompromised subjects to evaluate long-term immunity and the possibility of vaccine failure in this population.
6. Evaluation of immune status (e.g. CD4 counts) for vaccine recipients undergoing immunosuppressive therapy would allow better identification of risk groups for vaccine failure.
7. Direct comparison and stratification of immunosuppressive therapies in vaccine recipients
8. Evaluation of additional doses to demonstrate whether or not there is improved immunogenicity in immunocompromised populations.
9. Further direct comparisons of vaccination before and after transplantation.
10. Evaluate the effectiveness of HPV vaccine when administered following loop electrosurgical excision procedure (LEEP) to prevent recurrence of cervical intraepithelial neoplasia.
11. Identify the optimal HPV immunization schedule for persons 15 years of age and older.
12. Evaluate the immunogenicity and effectiveness of a 1-dose immunization schedule for HPV9 vaccine
13. Can protection against HPV-related disease be optimised by adding 1 or 2 doses of HPV9 vaccine to individuals who are fully immunized with HPV2 or HPV4?

VIII. SURVEILLANCE ISSUES

Ongoing and systematic data collection, analysis, interpretation and timely dissemination are fundamental to planning, implementation, evaluation, and evidence-based decision-making. To support such efforts, NACI encourages surveillance improvements in the following areas:

- Incidence and prevalence of both HPV infection and disease
- Distribution of HPV in high-risk populations in Canada (e.g. immunocompromised populations)
- Determining the potential for changes to cervical cancer screening recommendations, (e.g. lengthened screening intervals, change in age at initiation and termination, etc.) requiring a co-ordinated surveillance efforts and linkage between vaccine registries, cancer registries, screening registries and sexually transmitted infection surveillance

Laboratory

- HPV type distribution (e.g. monitor for type replacement, distribution of types in the Canadian population and in subpopulations thereof)

Vaccine

- Immunization coverage (including coverage in recommended groups such as men who have sex with men, which relies on self-identification prior to sexual debut)
- Safety

Attitudes and behaviours

- Perceptions of vulnerability to disease
- Attitudes toward vaccination
- Cervical screening behaviour

TABLES

Table 5. Summary of evidence related to HPV9 2-dose schedule

Non-peer-reviewed evidence						
Evidence for immunogenicity of HPV9 vaccine with 2-dose schedule						
STUDY DETAILS					**SUMMARY**	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Merck Protocol V503-010 NCT01984697 (unpublished)[3, 4]	HPV9 vaccine Gardasil®9	RCT Open-label International multicenter (52 sites in 15 countries including Canada) December 2013-June 19, 2015 37 month study	n=1518 enrolled 301 females (9-14 years) 2-dose (0,6mo) 301 males (9-14 years) 2-dose (0,6mo) 301 females/males (9-14 years) 2-dose (0,12mo) 301 females (9-14 years) 3-dose (0,2,6mo) 314 females (16-26 years) 3-dose (0,2,6mo)	37 month study with 3-dose schedule of 0,2,6 months or 2-dose schedules of 0, 6 and 0,12 months. Seroconversion and GMTs assessed 1 month after last dose. The non-inferiority criterion was met if the lower bound of two-sided 95%CI for GMT ratios of 2-dose/3-dose was greater than 0.67 Refer to Tables 3 and 4 for GMTs and seroconversion rates by HPV type, respectively. *Females and males (9-14 years)* *2-dose schedule (**0, 6 months**)* Seroconversion rates exceeded 99% against all 9 HPV vaccine types. GMTs non-inferior for all 9 HPV vaccine types 1 month after last dose in males and females 9-14 years old (with 2 doses) compared to females 16-26 years old who received 3 doses. *Combined females/males (9-14 years)* *2-dose schedule (**0,12 months**)*	I	Good (subjected to NACI modified peer-review process for non-peer-reviewed evidence)

Non-peer-reviewed evidence

Evidence for immunogenicity of HPV9 vaccine with 2-dose schedule

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of***	***Quality***
				Seroconversion rates of 100% against all 9 HPV vaccine types. GMTs against all 9 HPV vaccine types in this group of young boys/girls were non-inferior compared to the women who received 3 doses (0,2,6 months) of HPV9 vaccine.		

Evidence for safety of HPV9 vaccine with 2-dose schedule

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Merck Protocol V503-010 NCT01984697 (unpublished)[3, 4]	HPV9 vaccine Gardasil®9	RCT Open-label International multicenter (52 sites in 15 countries including Canada) December 2013-June 19, 2015 37 month study	n=1518 enrolled 301 females (9-14 years) 2-dose (0,6mo) 301 males (9-14 years) 2-dose (0,6mo) 301 females/males (9-14 years) 2-dose (0,12mo)	37 month study with 3-dose schedule of 0,2,6 months or 2-dose schedules of 0, 6 and 0,12 months. Safety assessed in 1496 subjects. Overall, HPV vaccine well-tolerated with for all schedules. *Females (n=294) and males (n=296) (9-14 years)* *2-dose schedule (**0, 6 months**)* No vaccine-related deaths, AEs or SAEs *Combined females/males (9-14 years)* *2-dose schedule (**0,12 months**)* *n=293* No vaccine-related deaths or SAEs. One AE (urticarial) resulted in discontinued schedule.	I	Good (subjected to NACI modified peer-review process for non-peer-reviewed evidence)

Evidence for safety of HPV9 vaccine with 2-dose schedule						
STUDY DETAILS					**SUMMARY**	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of***	***Quality***
			301 females (9-14 years) 3-dose (0,2,6mo) 314 females (16-26 years) 3-dose (0,2,6mo)	*Females (n=300) (9-14 years)* *3-dose schedule (**0,2,6 months**)* No vaccine-related deaths, AEs or SAEs. *Females (n=313) (16-26 years)* *3-dose schedule (**0,2,6 months**)* No vaccine-related deaths, AEs or SAEs.		

Table 6. Levels of Evidence Based on Research Design

Level	Description
I	Evidence from randomized controlled trial(s).
II-1	Evidence from controlled trial(s) without randomization.
II-2	Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group using clinical outcome measures of vaccine efficacy.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

Table 7. Quality (internal validity) Rating of Evidence

Quality Rating	Description
Good	A study (including meta-analyses or systematic reviews) that meets all design- specific criteria* well.
Fair	A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion* but has no known "fatal flaw".
Poor	A study (including meta-analyses or systematic reviews) that has at least one design-specific* "fatal flaw", or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.

* General design specific criteria are outlined in Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 2001;20:21-35.

Table 8. NACI Recommendation for Immunization -- Grades

Grade	Recommendation
A	NACI concludes that there is **good** evidence to recommend immunization.
B	NACI concludes that there is **fair** evidence to recommend immunization.
C	NACI concludes that the existing evidence is **conflicting** and does not allow making a recommendation for or against immunization; however other factors may influence decision-making.
D	NACI concludes that there is **fair** evidence to recommend against immunization.
E	NACI concludes that there is **good** evidence to recommend against immunization.
I	NACI concludes that there is **insufficient** evidence (in either quantity and/or quality) to make a recommendation, however other factors may influence decision-making.

LIST OF ABBREVIATIONS

Abbreviation	***Term***
AE	Adverse event
AGW	Anogenital warts
CD4	Cluster of differentiation 4
CIN	Cervical intraepithelial neoplasia
cLIA	Competitive Luminex Immunoassay
GMT	Geometric Mean Titre
GSK	GlaxoSmithKline
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HPV2 vaccine	Two-valent HPV vaccine (types 16, 18)
HPV4 vaccine	Four-valent HPV vaccine (types 6, 11, 16, 18)
HPV9 vaccine	Nine-Valent HPV vaccine (types 6, 11, 16, 18, 31, 33, 45, 52, 58)
HPV WG	Human Papillomavirus Working Group
mMU	milli-Merck Units
NACI	National Advisory Committee on Immunization
PHAC	Public Health Agency of Canada
RCT	Randomized control trial
SAE	Serious adverse event
µg	Microgram

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