

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

Updated Recommendations on Human  
Papillomavirus (HPV) Vaccines: 9-valent HPV  
vaccine and clarification of minimum intervals  
between doses in the HPV immunization schedule

*Please note that an erratum was completed following the July 2016 publication of this statement. Please see Introduction section for further details.*

PROTECTING CANADIANS FROM ILLNESS



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Également disponible en français sous le titre :

Recommandations mises à jour sur les vaccins contre le virus du papillome humain (VPH) : vaccin nonavalent contre le VPH et précisions sur les intervalles minimums entre les doses dans le calendrier d'immunisation contre le VPH

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## PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (hereafter referred to as the Agency) with ongoing and timely medical, scientific, and public health advice relating to immunization. The Agency 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 the Agency'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 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. HPV types 16 and 18 cause approximately 70% of cervical cancers. HPV types 31, 33, 45, 52, and 58 account for approximately 15-19% of cervical cancers<sup>(1-3)</sup>.

Low-risk HPV types can cause condylomata acuminata, also called anogenital warts (AGWs). Most cases (>90%) of AGWs are attributable to HPV types 6 and 11.

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 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 anogenital cancers and related pre-cancerous lesions, and AGWs associated with the HPV types included in the vaccine.

A recent phase II/III study of HPV9 vaccine demonstrated non-inferior immunogenicity for HPV types 6, 11, 16 and 18 compared to HPV4 vaccine, and high efficacy for the five additional HPV types (31, 33, 45, 52, and 58) contained in the vaccine. The safety profile of the HPV9 vaccine was comparable to the HPV4 vaccine, although adverse events related to injection site (mild-moderate intensity) were more common in the HPV9 vaccine compared to the HPV4 vaccine.

### 2. Who

#### Girls and Women

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 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.

Recently, HPV2 and HPV4 vaccines have also been authorized to be given as **two** separate 0.5 mL doses in younger 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)
- Studies of alternate dosing schedules for HPV9 vaccine are ongoing.

NACI recommendations:

- **HPV2, HPV4 or HPV9 vaccine is recommended** for routine vaccination of **females aged 9 to 26 years** and **may be used** in **females over 26 years** of age who have not been vaccinated previously or who have not completed the series.
- **HPV4 or HPV9 vaccine is recommended** for routine vaccination of **males aged 9 to 26 years**, and **may be used** in **males over 26 years** of age who have not been vaccinated previously or who have not completed the series.
- **HPV2 (in immunocompetent females 9-14 years of age) or HPV4 (in immunocompetent females or males 9-14 years of age) vaccine may be administered using either a 2-dose or 3-dose.** For a two-dose schedule, two separate 0.5 mL doses should be administered at months 0 and 6-12. *There is insufficient evidence at this time to recommend a 2-dose schedule for HPV9 vaccine. However, studies are ongoing and new evidence will be assessed as it becomes available.*
- **Any immunocompromised individual, immunocompetent HIV infected individuals,** and individuals who have not received any dose of HPV vaccine by 15 years of age should continue to receive **three doses** of HPV vaccine.

**Efforts should be made to administer HPV vaccines at the recommended intervals. When an abbreviated schedule is required, minimum intervals between vaccine doses should be met.** 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.***

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.

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 either HPV4 or HPV9 vaccine can prevent approximately 90% of AGWs (HPV types 6 and 11). Immunization with HPV9 vaccine 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.

## I. INTRODUCTION

**Erratum following publication on July 07, 2016. (Please note that changes have been made in the respective sections of this document)**

In Table 2, there were numerical errors in the “World: HPV prevalence” column for HPV types 6/11/16/18. The true values have been updated, changing some rates by 0-3%. The world prevalence of HPV types for penile cancer are listed as 16/18, not including low-risk non-oncogenic types 6/11.

On page 14, line 3, the HPV type 16 and 18 prevalence in vaginal cancers was previously listed as 14.8%, when the true number is 42.8%.

In February 2015, a nine-valent human papillomavirus vaccine (HPV9) (Gardasil®9, Merck Canada, Inc.) was authorized for use in Canada. The purpose of this statement is to summarize information on this vaccine and to provide evidence-based recommendations on its use in the context of recommendations for all HPV vaccines currently authorized for use in Canada. In addition, this statement will clarify minimum intervals between doses of HPV vaccines for two-dose and three-dose HPV immunization schedules.

In 2007, the national HPV immunization program goal was to decrease the morbidity and mortality of cervical cancer, its precursors and other HPV-related cancers in women in Canada.<sup>(3)</sup> This goal was expanded in 2014 to include the HPV-related burden of disease from conditions other than cancer in both males and females. The current national HPV immunization goal is to reduce vaccine- preventable HPV- related morbidity and mortality in the Canadian population.<sup>(4)</sup>

All jurisdictions in Canada are currently offering HPV immunization in publicly-funded programs to females in grades 4, 5, 6, 7 or 8. (Details on these programs are available at: <http://www.phac-aspc.gc.ca/im/is-vc-eng.php>). Several provinces have expanded their HPV programs to include males including: Prince Edward Island (2013), Alberta (2014), British Columbia (high risk program, 2015), Nova Scotia (2015). Manitoba and Quebec have announced plans to initiate expansion of their HPV programs to include males in the 2016/17 school year (<http://www.gov.mb.ca/health/publichealth/cdc/vaccineeligibility.html>; <http://www.fil-information.gouv.qc.ca/Pages/Article.aspx?aiguillage=ajd&type=1&idArticle=2312038377>).

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 anogenital cancer and related pre-cancerous lesions. 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) has recently been authorized for use in Canada for the prevention of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 -related anogenital cancers, related pre-cancerous lesions and AGWs. Gardasil®9<sup>(5)</sup> (HPV9 vaccine) is indicated in **girls and women, 9 through 45 years of age**, for the prevention of infection caused by the HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 and the following diseases associated with the HPV types included in the vaccine:

- Cervical, vulvar, and vaginal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58
- AGWs caused by HPV types 6 and 11
- Precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52,



and 58:

- Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 2 and grade 3
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- Cervical intraepithelial neoplasia (CIN) grade 1

In addition, Gardasil®9 is indicated in **girls and women 9 through 26 years of age** for the prevention of:

- Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3 caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

Gardasil®9 is indicated in **boys and men 9 through 26 years of age** for the prevention of infection caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 and the following diseases associated with the HPV types included in the vaccine:

- Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58
- AGWs caused by HPV types 6 and 11
- AIN grades 1, 2, and 3 caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58.

In Canada, the National Advisory Committee on Immunization (NACI) has recommended a 3-dose immunization schedule with HPV vaccine for females 9 years of age and older since February 2007, and for males between 9 and 26 years of age since January 2012.<sup>(6, 7)</sup>

Either HPV2 or HPV4 vaccines have been recommended for the prevention of cervical cancer and its precursors in females, including those who have had previous Papanicolaou (Pap) test abnormalities, cervical cancer or AGWs. HPV4 vaccine has also been recommended for the prevention of vulvar, vaginal, and anal cancers and their precursors, and AGWs in females, as well as anogenital cancer and AGWs in males. In its 2012 Advisory Committee Statement, NACI recommended a 3-dose HPV immunization schedule for both HPV2 and HPV4 vaccine.

HPV vaccines have been authorized 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. As of July 3, 2014, HPV2 vaccine has been authorized for use in girls from age 9 to 14 years of age at the time of first injection as a 2-dose schedule (0, 6 months). As of March 10, 2015, HPV4 vaccine has also been authorized for use in individuals from age 9 to 13 years of age as a 2-dose schedule (0, 6 months or 0, 12 months).

A 2-dose HPV immunization schedule among immunocompetent 9-14 year olds is expected to provide similar protective efficacy compared to a 3-dose schedule in immunocompetent individuals aged 9-26 years, and may be considered to allow for potential cost savings and other individual and programmatic advantages. In its February 2015 Advisory Committee Statement,<sup>(8)</sup> NACI recommended that a 2-dose HPV immunization schedule may be considered for the following groups, and assigned recommendation grades, based on the strength of the evidence available at the time:

**Table 1. NACI Recommendations for the HPV Immunization Schedule (2015)**

<b>RECOMMENDED GROUPS</b>	<b>RECOMMENDED IMMUNIZATION SCHEDULE</b>	<b>NACI RECOMMENDATION GRADE BASED ON EVIDENCE AVAILABLE</b> (see Table 9 for Grading descriptions)
<b>Healthy (immunocompetent, not infected with HIV) Females 9-14 years of age</b>	2- or 3-dose schedule (with HPV4 or HPV2)	Grade A
<b>Healthy (immunocompetent, not infected with HIV) Females ≥15 years of age</b>	3-dose schedule (with HPV4 or HPV2) (If first dose administered between 9-14 years of age, 2 doses are sufficient)	Grade A
<b>Healthy (immunocompetent, not infected with HIV) Males 9-14 years of age</b>	2- or 3-dose schedule (with HPV4)	Grade B
<b>Healthy (immunocompetent, not infected with HIV) Males ≥15 years of age</b>	3-dose schedule (with HPV4) (If first dose administered between 9-14 years of age, 2 doses are sufficient)	Grade B
<b>Immunocompromised individuals and immunocompetent HIV-infected individuals</b>	3-dose schedule (with HPV4 or HPV2 in females and with HPV4 in males)	Grade I

NACI recommends that, for a 2-dose schedule, the second dose of HPV vaccine be administered at least 6 months after the first. For a 3-dose HPV immunization schedule, NACI has recommended that the vaccines be administered at 0, at 1 or 2 months (depending on the vaccine), and at 6 months. The 2012 NACI Advisory Committee Statement Update on HPV Vaccines<sup>(4)</sup> and current Canadian Immunization Guide (CIG) HPV chapter<sup>(7)</sup> indicate that if an abbreviated schedule is required, a minimum interval of 4 weeks between dose 1 and dose 2, and a minimum interval of 12 weeks (HPV4 specified) between dose 2 and dose 3 is acceptable. No minimum interval between dose 1 and dose 3 is explicitly identified in the current HPV chapter of the CIG or the NACI statements.

A recent review of published evidence of the long term efficacy and safety of HPV2 and HPV4 vaccines that have been widely implemented in vaccination programs around the world,

primarily targeting adolescent girls, concluded that efficacy and safety of both vaccines have been well-established. The review included studies of the HPV2 vaccine with follow up of 9.4 years, and 8 years for the HPV4 vaccine, and found that the vaccine continues to be immunogenic and well tolerated up to 9 years following vaccination, and that all randomized controlled clinical trials of the two vaccines provide evidence of an excellent safety profile. Additionally, clinical effectiveness of existing vaccines has been demonstrated. A systematic review of early direct and indirect effects of HPV4 vaccine on AGWs summarized published evidence of a rapid reduction in the incidence of AGWs after implementation of the vaccination program, despite differences in study designs and populations studied. The review also provided some evidence of possible herd protection in unvaccinated populations of men and older females, most notably when vaccine coverage was high. However, certain populations, such as men who have sex with men (MSM), would not benefit from herd protection if immunization against HPV were restricted to females.<sup>(9)</sup>

This statement will:

- Provide information on the HPV9 vaccine and recommendations for its use;
- Review epidemiological data on the relative contribution of the 5 additional genotypes covered in the HPV9 vaccine to disease outcomes;
- Clarify acceptable minimum intervals between vaccine doses in either a 2-dose or 3-dose HPV immunization schedule.

## II. METHODS

### HPV9 vaccine

NACI reviewed the key questions for the literature review on HPV9 vaccine as proposed by the HPV Working Group, including: the burden of illness of the disease to be prevented and the target population(s), safety, immunogenicity, efficacy, effectiveness of the vaccine(s), vaccine schedules, and other aspects of the overall immunization strategy. The knowledge synthesis was performed by a resident in Public Health and Preventive Medicine, and supervised by a PHAC medical specialist and the Working Group. Following critical appraisal of individual studies, summary tables with ratings of the quality of the evidence using NACI's methodological hierarchy (Table 8) were prepared, and proposed recommendations for vaccine use were developed. The Working Group chair and PHAC medical specialist presented the evidence and proposed recommendations to NACI on June 10, 2015. Following thorough review of the evidence and consultation at the NACI meeting, the committee adopted specific recommendations. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the text.

A literature search and review of articles limited to the English language were completed. The search was not limited by any time interval. To identify studies evaluating the efficacy, immunogenicity and safety of the HPV9 vaccine, a systematic search of Medline, CINAHL, EMBASE and Google Scholar was conducted. Keywords included: papillomavirus vaccines, HPV adj\* vaccine, 9-valent, HPV9, Gardasil®, nonavalent, wart virus vaccine, and variations thereof. A total of 13 abstract articles obtained through the literature search were identified and reviewed. An additional 14 documents were provided by the manufacturer of the HPV9 vaccine, including one published journal article (also obtained through the literature search) and 13

poster or abstract presentations. Duplications, editorial articles and review articles were excluded. Articles that discussed cost effectiveness of the vaccine, potential impact of the vaccine based on modelling, development of immunoassays for HPV types and studies discussing prevalence of different HPV types were excluded. In addition, a presentation outlining studies in progress and available data was provided by the manufacturer of the HPV9 vaccine to NACI in October 2014 and to the NACI HPV Working Group (WG) in February and May 2015.

In making its recommendations, NACI and the HPV WG considered the evidence that had been reviewed by May 5, 2015, including: one published, peer-reviewed journal article; four unpublished studies presented in posters (protocols 005, 006, 007 and 009); and results from pivotal trials (protocols 002, 003, 005, 006, 007, 009) presented to NACI by the manufacturer. The reviewed evidence is included in the summary of evidence table (Table 6) and discussed in the text. The unpublished studies and protocols are clinical trials that use the same study population that was included in the published journal article. Due to the limited number of published, peer-reviewed journal articles currently available, unpublished data are included and interpreted with caution in this statement, as they have not been through the peer-reviewed process. Subsequent to the review, protocols 003<sup>(10)</sup>, 005<sup>(11)</sup>, 006<sup>(12)</sup>, 007<sup>(13)</sup>, and 009<sup>(14)</sup> have been published.

### **Minimum intervals between HPV vaccine doses in a 3- dose immunization schedule**

NACI reviewed the key questions for the literature review on acceptable minimum intervals between HPV vaccine doses as proposed by the HPV Working Group, including the specific question of the acceptable minimum interval between the first and last dose of HPV vaccine in a 3-dose schedule. The knowledge synthesis, including an environmental scan and literature review, was performed by a PHAC Research Analyst and PHAC Medical Specialist. Following critical appraisal of individual studies, summary tables with ratings of the quality of the evidence using NACI's methodological hierarchy (Table 8) were prepared, and proposed recommendations were developed. The Working Group chair, PHAC medical specialist, and PHAC Research Analyst presented the evidence and proposed recommendations to the NACI HPV WG on February 17, 2015. Following thorough review of the evidence and consultation at the NACI meeting on June 10, 2015, the committee adopted specific recommendations. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the text.

A literature search and review of articles limited to the English language were completed. The search was not limited by any time interval. A systematic search of Scopus, the Cochrane Library and Medline was conducted. Keywords included: vaccin\*, immuniz\*, immunis\*, inocul\*, Gardasil, cervarix, sched\*, interval\*, quadrivalent, bivalent, dos\*, schedule\*, interval\*, effective\*, efficac\*, protect\*, immunogenic\* OR antibod\*, seroconver\*, seropositiv\*, seronegativ\*, titre, gmt, gmc, noninferior\*, wart\*, neoplasia, cin3\*, cin2\*, cin1\*, infect\*, boy, girl, teen, adolescent, youth and variations thereof. Correspondence was initiated with both GSK and Merck to supplement the findings of a literature review. A total of 1546 articles were produced from the literature search and 10 records from additional sources. Duplications were excluded. 1153 titles and abstracts were screened, and 828 were irrelevant and so excluded. 325 full text and abstracts were screened, and 314 were irrelevant and so excluded. Eleven full text articles were identified and reviewed and are included in the summary of evidence table (Table 6) and discussed in the text.



### 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 <sup>(15-17)</sup>. 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.

#### **Estimated burden of HPV-related disease according to HPV type**

HPV infection is not reportable in Canada. Information on national pre-cancer and cancer incidence is available through the Canadian Cancer registry and the Pan-Canadian Cervical Cancer Screening Program. Data on the prevalence and attribution of specific HPV types to pre-cancerous lesions and cancer in Canada are limited, and are therefore estimated from large international studies. Two recently reported meta-analyses conducted by de Vuyst et al <sup>(18)</sup> and Guan et al <sup>(19)</sup> provide information on HPV genotype prevalence in pre-cancers and cancers of the anogenital region. The meta-analysis conducted by de Vuyst et al <sup>(18)</sup> investigated HPV prevalence in female and male genital carcinomas and precancerous lesions from 93 studies that were primarily conducted in Europe and North America. In a meta-analysis of 423 international studies conducted by Guan et al <sup>(19)</sup>, HPV type distribution was calculated based on the results from over 115,000 HPV-positive women, including more than 33,000 with normal cytology, 26,000 with pre-cancerous lesions, and 36,000 with invasive cervical cancers. The majority of studies included in the two meta-analysis were conducted before the implementation of the HPV immunization programs and therefore provide estimates of HPV- type prevalence, which may differ from those observed following the introduction of HPV vaccines containing high- risk types 16 and 18. Additional consideration was given to the estimates of relative contribution of HPV9 vaccine-contained types to cervical cancer and cervical precancerous lesions conducted by Serrano et al <sup>(20)</sup>, and those conducted for anal and vaginal cancers by Alemany et al <sup>(21)</sup>. Table 2 summarizes the incidence of major HPV-related cancer in Canada, based on the data from the Canadian Cancer Registry, as well as the prevalence of HPV types in cancer tissue and their estimated contribution to cancer, based on the data from the reviewed studies.



**Table 2. Average cancer incidence rates and estimated prevalence contribution of HPV9 vaccine contained HPV types\***

Cancer counts and rates (/100,000), Canada 2001 to 2010 combined						World					North America				
All histologies (1)						HPV prevalence					HPV prevalence				
Squamous cell (2)						Contribution of HPV types (3)					Contribution of HPV types (3)				
Sex	Site	Rate	Count	Rate	Count	Any	HPV 6/11/16/18	HPV 31/33/45/52/58	HPV 6/11/16/18	HPV 31/33/45/52/58	Any	HPV 6/11/16/18	HPV 31/33/45/52/58	HPV 6/11/16/18	HPV 31/33/45/52/58
Male	anus	1.4	205	0.7	100	84.3%	69.0%	6.0%	87.2%	8.0%				87.7%	9.0%
	penis	0.9	125	0.8	115	63.3%	47.9%†	9.0%							
Female	anus	1.9	285	1.3	200	84.3%	69.0%	6.0%	90.2%	7.9%				87.7%	9.0%
	vagina	0.8	115	0.4	65	69.9%	46.0%	7.8%	60.5%	20.5%				61.1%	24.1%
	vulva	2.6	385	1.9	290	40.4%	15.6%	2.5%							
	cervix	8.4	1280	8.1	1225	89.4%	70.0%	19.4%	70.9%	18.5%	89.6%	72.4%	20.0%	78.8%	16.7%
	CIN2/3	580				90.5%	55.5%	42.0%	57.1%	41.4%	93.9%	62.3%	40.0%	66.3%	42.6%
	Cervix normal cytology	-				12.4%	3.6%	4.0%			21.1%	7.5%	6.0%		

\*the contribution of HPV 31/33/45/52/58 types to head and neck cancers in Canada is estimated at less than 1% and is not reported

†the world prevalence of HPV types for penile cancer are listed as 16/18, not including low-risk non-oncogenic types 6/11.

(1) All histologies excluding sarcomas, lymphomas, leukaemias and mesothelial cancers

(2) Cervix: ICD-O-3 histology codes 8010-8671, 8940-8941; Other cancer types: squamous cell carcinomas defined as ICD-O-3 histology codes 8050-084, 8120-8131.

(3) Prevalence estimates of genotypes 6/11/16/18/31/33/45/52/58 not mutually exclusive as multiple HPV types may contribute to cancer development

High-risk HPV types 16 and 18 have been estimated to cause up to 78.8% of cervical cancers, 66.3% of high-grade cervical dysplasia, and 90.2% of anal carcinomas. In addition, infection with these HPV types is also present in up to 47.9% of penile and 42.8% of vaginal cancers. Attribution of five additional high-risk types contained in HPV9 vaccine (31, 33, 45, 52 and 58) to cervical cancer has been estimated to range between 16.7% and 18.5%, and up to 24.1% for vaginal cancer, 9% for anal and penile cancer, and 2.5% for vulvar cancer. A recently conducted meta-analysis by Ndiaye et al<sup>(22)</sup> that included data from over 12,000 cases, suggests a contribution of 23.6% of HPV types contained within the HPV4 vaccine, and a very low contribution (1%) of the additional 5 types contained within the HPV9 vaccine to squamous cell carcinoma of the head and neck. Types contained in HPV4 vaccine have also been estimated to contribute approximately two-thirds of CIN 2/3 (high-grade cervical intraepithelial neoplasia and adenocarcinoma in situ) cases, whereas the additional five types in HPV9 vaccine contribute approximately one-third of CIN 2/3 cases.

The disease burden associated with the five additional genotypes contained in HPV9 vaccine is not equally shared between the sexes, with the additional benefit primarily observed among females. If the entire population for whom the vaccine is indicated is immunized and there is one hundred percent efficacy, immunization with HPV9 vaccine in Canada, in addition to annually averting approximately 1,600 anogenital cancers associated with HPV types 16 and 18, could prevent up to 320 anogenital cancers (300 in females and 20 in males). HPV9 vaccination also can lead to further reduction of high (CIN 2/3) and low-risk (CIN 1) cervical lesions in females. Immunization against the five additional types contained in HPV9 vaccine would not result in a further reduction of AGWs, because there are no additional HPV types in the vaccine that prevent AGWs. Such estimates are similar to those recently documented by the Advisory Committee on Immunization Practices (ACIP), which concluded that, in the United States of America, approximately 64% of invasive HPV-associated cancers are attributable to HPV 16 or 18 (65% for females; 63% for males) and 10% are attributable to HPV 31, 33, 45, 52, 58 (14% for females; 4% for males).

The detailed epidemiology of HPV in Canada and estimated reductions of HPV2 and HPV4 vaccine associated cancers have previously been published in the Update on HPV Vaccines<sup>(8)</sup> released in January 2012. Additional information on symptoms and natural progression of disease can be found in the Canadian Immunization Guide (CIG) (<http://www.phac-aspc.gc.ca/publicat/cig-gci/>).

## IV. 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 3.

**Table 3. Comparison of HPV Vaccines Authorized for Use in Canada**

	<b>CERVARIX® (HPV2)</b>	<b>GARDASIL® (HPV4)</b>	<b>GARDASIL®9 (HPV9)</b>
<b>Immunogens (Recombinant L1 proteins from HPV types:)</b>	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
<b>Manufacturer</b>	GlaxoSmithKline Inc.	Merck Canada Inc.	Merck Canada Inc.
<b>Authorization</b>	<ul style="list-style-type: none"> <li>females 9-45 years</li> </ul>	<ul style="list-style-type: none"> <li>females 9-45 years</li> <li>males 9-26 years</li> </ul>	<ul style="list-style-type: none"> <li>females 9-45 years</li> <li>males 9-26 years</li> </ul>
<b>Antigen Components (µg):</b>			
<b>HPV type 18 L1 protein</b>	20	20	40
<b>HPV type 16 L1 protein</b>	20	40	60
<b>HPV type 11 L1 protein</b>		40	40
<b>HPV type 6 L1 protein</b>		20	30
<b>HPV type 31 L1 protein</b>			20
<b>HPV type 33 L1 protein</b>			20
<b>HPV type 45 L1 protein</b>			20
<b>HPV type 52 L1 protein</b>			20
<b>HPV type 58 L1 protein</b>			20
<b>Adjuvant</b>	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)
<b>Other ingredients</b>	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

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 response among different age groups to antigens in the vaccine. The underlying premise of immunobridging 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.

The results of a phase II/III study conducted to determine immunogenicity, efficacy, and safety of the HPV9 vaccine in women 16 to 26 years of age have recently been published <sup>(23)</sup>. In this randomized, controlled, international, multi-centre, double-blind study<sup>(23)</sup> involving 14,215 participants, HPV4 vaccine was used as an active comparator, as the use of placebo was not considered to be acceptable for ethical reasons. The baseline characteristics were similar in the two vaccination groups. Vaccines were administered in three doses, on day 1 and at month 2 and month 6. All participants received a vaccination report card on which they recorded oral temperatures on each of the 5 days after vaccination and adverse events related to the injection site, as well as systemic adverse events on each of the 15 days after vaccination. Swabs of labial, vulvar, perineal, perianal, endocervical, and ectocervical tissue and Pap test samples were collected on day 1 and at months 7, 12, 18, 24, 30, 36, 42, 48, and 54. Swabs were tested for HPV types 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 by means of a polymerase-chain-reaction (PCR) assay to identify participants who had an active HPV infection at enrollment and to determine end points for HPV infection.

Successful demonstration of the primary efficacy hypothesis required the lower boundary of the two-sided 95% confidence interval of vaccine efficacy to be greater than 25%, where vaccine efficacy, or percent risk reduction, was calculated as  $100 \times (1 - \text{incidence rate of types in HPV9} \div \text{incidence rate of types in HPV4})$ . Successful demonstration of the primary immunogenicity hypothesis of non-inferiority required the lower boundary of the two-sided 95% confidence interval of the ratio of the geometric mean titre (GMT) (HPV9:HPV4) to be greater than 0.67 for each of the anti-HPV types 6, 11, 16, and 18. Supportive efficacy analyses were performed in the intention-to-treat population <sup>(23)</sup>.

In the comparison of HPV9 and HPV4 vaccination per-protocol efficacy groups, the risk reduction for disease related to HPV-31, 33, 45, 52, and 58 was 96.7% (95% confidence interval, 80.9 to 99.8) and 96.3 (95% confidence interval, 79.5 to 99.8) for high-grade cervical, vulvar, and vaginal disease, and for high-grade cervical epithelial neoplasia, adenocarcinoma in situ and cervical cancer respectively. The risk reduction for persistent infection, greater than or equal to 6 months, was 96.0% (95% confidence interval, 94.4 to 97.2). The single participant with HPV-58–positive grade 2 cervical epithelial neoplasia in the HPV9 vaccine group had positive results for HPV-56 at baseline and in all specimens obtained between day 1 and the time of diagnosis, with HPV-58 detected only at the time of diagnosis. In contrast, the incidence of high-grade cervical, vulvar, and vaginal disease in the HPV4 caused by these five additional genotypes in HPV9 vaccine continued to increase over time <sup>(23)</sup>.

In the comparison of HPV9 and HPV4 vaccination intention-to-treat groups, the average risk reduction was 19.0% (95% confidence interval, –1.6 to 35.3) and 17.1% (95% confidence interval, –4.2 to 34.0) for high-grade cervical, vulvar and vaginal disease and for high-grade cervical epithelial neoplasia, adenocarcinoma in situ and cervical cancer respectively. The risk



reduction for those uninfected by HPV at day 1 and for disease related to the nine vaccine HPV types was 100% (95% confidence interval, 70.4 to 100) and 100% (95% confidence interval, 70.3 to 100) for high-grade cervical, vulvar and vaginal disease and for high-grade cervical epithelial neoplasia, adenocarcinoma in situ and cervical cancer respectively <sup>(23)</sup>.

A poster presentation at the International Papillomavirus Conference in August 2014 summarized an exploratory analysis of the potential for the HPV9 vaccine to decrease the overall risk of cervical, vulvar and vaginal disease. The risk reduction of disease was assessed compared to a historic placebo cohort from the HPV4 vaccine program. Significant risk reductions in CIN1 (44%), CIN2+ (63%), and AGWs (86%), and marginally significant reductions in risk of VIN1 or VaIN 1 (52%) were reported. The poster reported significant reductions in risk of Pap test abnormalities (ASCUS HR HPV positive or worse) of 44.3% and high-grade lesions (atypical squamous cells of high grade [ASC-H] or worse) of 63.8%. Significant risk reductions in cervical biopsies (28%) and cervical definitive therapy (47%) were observed.

### **Use of HPV9 vaccine in prior HPV4 vaccine recipients**

The efficacy of HPV9 vaccine in preventing infection and disease related to HPV types 31, 33, 45, 52, and 58 in individuals previously immunized with HPV4 vaccine has not been assessed.

## **IV.3 Immunogenicity of HPV9 vaccine**

### ***Females***

For the published phase II/III study<sup>(23)</sup> (methods and design described in “IV.1a Efficacy of HPV9 Vaccine”), the outcome measures used to calculate immunogenicity were GMT and seroconversion. According to the GMT, the non-inferiority of the response to the HPV9 vaccine as compared with the response to the HPV4 vaccine for HPV-6, 11, 16, and 18 was established at 1 month after dose 3. Numerically, the ratios for GMT for HPV types 6, 11, 16, and 18 ranged from 0.80 to 1.19, with ratios close to 1 for HPV-6 and 16, greater than 1 for HPV-18, and lower than 1 for HPV-11.

A study presented to NACI in October 2014 (Protocol 002) focused on adult to adolescent immunobridging. This open label study was conducted on 1,800 girls (9-12 years: n~1200; 13-15 years: n~600), 600 boys (9-12 years: n~400; 13-15 years: n~200) and 400 young women (16-26 years). The objective was to compare the immunogenicity of HPV9 vaccine in male and female youth (9-15 years of age) vs. young women (16-26 years of age). Subjects were vaccinated on day 1, month 2, and month 6. Immunogenicity was assessed for genotypes 6, 11, 16, 18, 31, 33, 45, 52, and 58, and was assessed at day 1 and month 7. The non-inferiority criterion for seroconversion was met for all 9 HPV types ( $P < 0.001$ ), for boys and girls, when compared to women. Seroconversion rates were > 99% in all instances.

The results of a double-blinded, randomized, controlled trial focusing on immunogenicity of HPV9 in girls aged 9 to 15 (Protocol 009) was presented to NACI in October 2014. Participants were vaccinated with HPV9 (n = 300) or HPV4 (n = 300) on day 1, and at months 2 and 6. The GMT ratios for genotypes 6,11,16 and 18 were 1.07, 0.93, 0.97 and 1.08 respectively and met the non-inferiority criteria in that the lower bound of the 95% CI for each ratio was greater than 0.67. The immune responses for genotypes 6, 11, 16 and 18 were comparable in adolescent girls who received HPV9 vs adolescent girls who received HPV4.



## **Males**

Protocol 003 was presented to the NACI HPV Working Group in February 2015 and had the objectives to demonstrate non-inferior immunogenicity of HPV9 vaccine among heterosexual men 16 to 26 years (n= 1103) vs women 16 to 26 years (n=1099) and to summarize immunogenicity of HPV9 vaccine among 300 MSM. The non-inferiority criterion was met for all nine HPV types ( $P<0.001$ ) for heterosexual men vs women. The GMTs were lower among MSM vs heterosexual men in a 0.6 to 0.7 range, which is similar to GMT ratios observed with HPV4 for MSM vs heterosexual men. The reason for this finding is unknown. The seroconversion rate for MSM was greater than 99%.

## **Use of HPV9 in prior HPV4 vaccine recipients**

Protocol 006 (n = 900) aimed to evaluate immunogenicity and safety of HPV9 vaccine in young girls and women who had previously received HPV4. GMTs quantified with the use of competitive Luminex immunoassay (cLIA) were measured at day 1, month 2 (post-dose 1) and month 7 (post-dose 3). Prior to enrolment in the study, over 99% of subjects had received three doses of HPV4 vaccine within a one year period. The time interval between the last and the first dose of HPV9 vaccine ranged from approximately 12 to 36 months. At 4 weeks post-dose 3, over 98% of subjects in the HPV9 vaccine cohort were seropositive for HPV types 31, 33, 45, 52, and 58. In the group vaccinated with HPV9, GMTs for HPV types 6, 11, 16 and 18 increased markedly post-dose 1 and remained at similar levels post-dose 2 and 3 (consistent with a memory response to these 4 HPV types in prior HPV4 vaccine recipients), whereas GMTs for HPV types 31, 33, 45, 52 and 58 increased after dose 1, and increased further after doses 2 and 3 (consistent with a primary response to these additional 5 HPV types contained in HPV9 vaccine). Past vaccination with HPV4 did not prevent seroconversion to genotypes 31, 33, 45, 52 and 58. The level of significance and confidence intervals were not provided for these findings. In a cross-study analysis, anti-HPV 31, 33, 45, 52, and 58 GMTs among those previously vaccinated with HPV4 were lower than in subjects' naïve to HPV4 (comparison group drawn from Protocol 001) who were administered HPV9 vaccine. The clinical significance of this finding is unknown.

## **IV.5 Vaccine Administration and Schedule**

### ***Vaccine Administration***

HPV9 vaccine is administered by intra-muscular injection. Gardasil® 9 is authorized for use as a 3-dose schedule at 0, 2, and 6 months.

### ***Minimum Intervals between doses of HPV vaccines in a 3 dose immunization schedule***

Product monographs issued by the vaccine manufacturers indicate that some flexibility in the minimum dosing intervals will not substantially affect immune responses to 3-dose regimens of HPV vaccines. The product monograph for Gardasil® 9 states that “[i]ndividuals are encouraged to adhere to the 0, 2, and 6 months vaccination schedule. If an alternate vaccination schedule is necessary, the second dose should be administered at least 1 month after the first dose, and the third dose should be administered at least 3 months after the second dose.”<sup>(5)</sup> Indeed, shortened ‘flexibility range’ dose intervals have historically been used with HPV vaccines in a small proportion of patients. However, there is a paucity of published evidence supporting

shortened or flexible minimum intervals, compared to ample evidence endorsing the recommended schedules, as well as evidence supporting delays in the receipt of booster doses. Assumptions about the immunogenicity and efficacy of shortened 'flexibility range' minimum dose intervals rely heavily on the manufacturer's unpublished data on file and their Health Canada-approved recommendations included in the product monographs.

### **Interval between Dose 1 and Dose 3 of HPV vaccines**

Results from several retrospective studies (see Summary of Evidence Table 6) indicate that <5% of females receiving 3 doses of HPV vaccine in the USA prior to 2010 were immunized on a dose schedule that breaches the minimum recommended interval between doses 1 and 3<sup>(24-26)</sup>.

Evidence from the bivalent vaccine manufacturer's post-hoc analysis of clinical study data indicates that a shortened 1-3 dose interval of 5 months results in similar anti-HPV16 and 18 antibody titres compared to the recommended 6 month interval when measured one month after the final dose. However, non-inferiority has not been explicitly indicated, nor has duration of immunity.

Several clinical studies have explored HPV vaccine immunogenicity and efficacy using the manufacturer's recommended minimum dose interval or the shorter 'flexibility range'. However, results from these studies are not stratified by dose interval, and therefore it is not possible to comment on the specific success or non-inferiority of implementing the shortened interval that falls within the 'flexibility range' for either the bivalent or quadrivalent HPV vaccine.

In conclusion, the evidence to support a shortened dose interval (less than 6 months) between doses 1 and 3 of the 3-dose HPV vaccine series is weak.

### **Interval between Dose 1 and Dose 2 of HPV vaccines**

Retrospective studies indicate that <1% of females receiving 3 doses of HPV vaccine in the USA prior to 2010 were immunized on a dose schedule that breaches the minimum recommended interval between doses 1 and 2.<sup>(24, 25)</sup>

When dose 2 of HPV4 vaccine was administered 1 month early on a 0, 1, 6 month schedule (within the manufacturer's 'flexibility range'), it was shown to elicit cross-neutralizing antibodies against non-vaccine HPV types in serum and genital secretions at 1 and 6 months after the final dose<sup>(27)</sup>. Both HPV4 and HPV2 vaccines elicited high titres of neutralizing antibodies against HPV 16 and 18, but the response magnitude was greater with HPV2 vaccine, which was administered with recommended dosing (0, 1, 6 months), compared to HPV4 vaccine.

In conclusion, the evidence to support a shortened dose interval (less than 2 months) between doses 1 and 2 of the quadrivalent 3-dose HPV vaccine series is weak. In addition, there is no published evidence to support or to refute a shortened dose interval (less than 1 month) between doses 1 and 2 of the bivalent vaccine.

Since October 2014, NACI has recommended a minimum interval of 24 weeks (6 months) between the first and second dose in a 2 dose schedule with either HPV2 or HPV4.

### Interval between Dose 2 and Dose 3 of HPV vaccines

Retrospective studies indicate that <3% of females receiving 3 doses of HPV vaccine in the USA prior to 2010 were immunized on a dose schedule that breaches the minimum recommended interval between doses 2 and 3<sup>(24-26)</sup>.

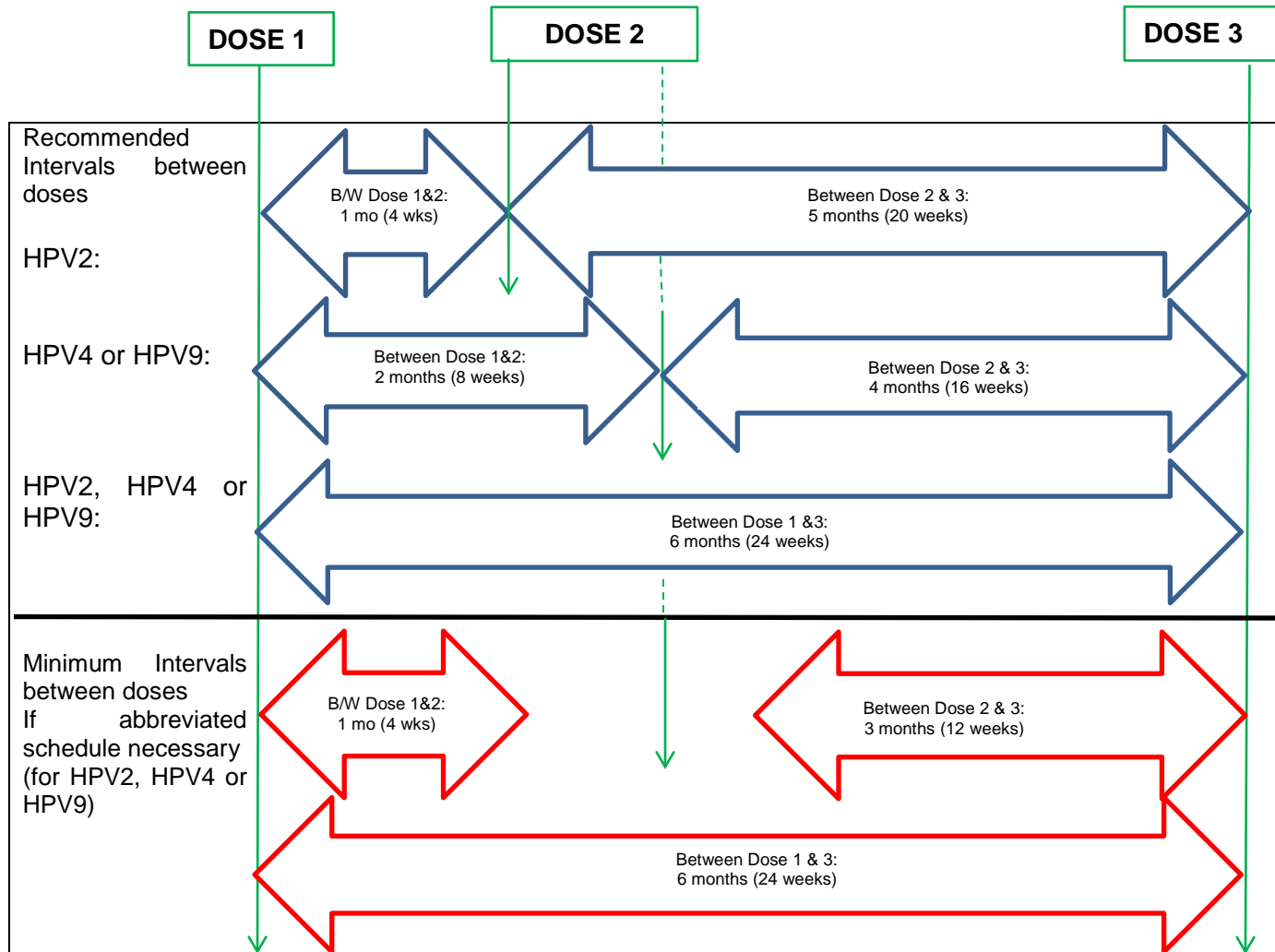
Evidence from the bivalent vaccine manufacturer's post-hoc analysis of clinical study data indicates that using an alternate schedule (0, 2, 6 months) with a shortened 2-3 dose interval of 4 months results in similar anti-HPV16 and 18 antibody titres compared to the recommended 5 month interval when measured one month after the final dose. However, non-inferiority has not been explicitly indicated and the results were drawn from a small sample subset (n=61-70) of the larger trial. In addition, duration of immunity was not assessed.

Several clinical studies have explored HPV vaccine's immunogenicity and efficacy using the manufacturer's recommended minimum dose interval or the shorter 'flexibility range'. However, results from these studies are not stratified by dose interval, and therefore it is not possible to comment on the specific success or non-inferiority of implementing the shortened interval that falls within the 'flexibility range' for either the bivalent or quadrivalent HPV vaccine.

In conclusion, the evidence to support a shortened dose interval (less than 5 months) between doses 2 and 3 of the bivalent 3-dose HPV vaccine series is weak, and there is no published evidence to support or to refute a shortened dose interval (less than 4 months) between doses 2 and 3 of the quadrivalent vaccine.

Recommended intervals, and minimum intervals that are to be used only if an abbreviated schedule is unavoidable, between doses in a 3 dose HPV immunization schedule are summarized in Figure 1.

**Figure 1. Recommended Intervals and Minimum Intervals (if an abbreviated schedule is necessary) between doses in a 3- Dose HPV Immunization Schedule**



## IV.7 Storage Requirements of HPV Vaccines

According to the product monograph, Gardasil®9 (like HPV4 and HPV2) should be refrigerated at +2 to +8°C, should not be frozen, and should be protected from light. It should be administered as soon as possible after being removed from refrigeration. The product should be discarded if it is frozen, if particulates are present, or if it appears discoloured.

Thermostability data indicate that these vaccines are very stable, which is an important consideration in the event of a cold chain break. An evaluation of the thermostability data of HPV4 using an enzyme immunoassay, [in vitro relative potency (IVRP) assay] and differential scanning calorimetry (DSC) found that the antigens in the vaccine are highly stable, and that at temperatures up to 25°C, the vaccine is stable for periods of 130 months or longer. The study suggests that even at temperatures of 37° to 42° C, the vaccine will likely retain more than 50% of the initial potency for several months. The study indicated that the aluminum adjuvant significantly stabilizes the VLPs. Similarly, data submitted to the European Medicines Agency (EMA) for HPV9 vaccine supported Time out of Refrigeration (TOR) allowances of 10 days at 25°C and one day at 37°C. However, to minimize the risk of uncontrolled product storage and subsequent deterioration, only TOR allowances of 72 hours (when stored at temperatures from 8°C to 25°C or from 0°C to 2°C) were subsequently approved by EMA, with the instruction to use or discard the product at the end of this period.

The product monograph states that Gardasil®9 (like Gardasil®) can be administered if the total (cumulative multiple excursion) time out of refrigeration (at temperatures between 8°C and 25°C) does not exceed 72 hours. Cumulative multiple excursions between 0°C and 2°C are also permitted as long as the total time between 0°C and 2°C does not exceed 72 hours.<sup>(5)</sup> The product monograph for Cervarix® indicates that the vaccine remains stable and can be administered in the event that the vaccine has been stored outside the refrigerator for up to 72 hours at temperatures between 8°C and 25°C or up to 24 hours at temperatures between 25°C and 37°C. If exposed to temperatures >37°C, the vaccine should be discarded.

## IV.8 Simultaneous Administration of HPV9 Vaccine with Other Vaccines

An open-label, randomized, immunogenicity and safety study of HPV9 vaccine administered concomitantly with Menactra® and Adacel™ (Protocol 005) involved serological testing of 1,237 participants at day 1, at month 1, 2 (control group only), and at month 7. The non-inferiority criterion was met for all 9 HPV types ( $P < 0.001$ ), with a 100% seroconversion rate. The non-inferiority criteria were met for *N. meningitidis* serogroups, antipertussis responses and diphtheria and tetanus titers. These findings suggest that there is no interference with the antibody response to any of the vaccine's antigens. The frequencies of adverse events were comparable between the two groups (90.7% for the concomitant group and 88.7% for the non-concomitant group.) The level of significance and confidence intervals were not provided. The frequency of serious adverse events was the same for both groups (0.8%), and no serious adverse events or deaths were assessed to be caused by the vaccine.

Concomitant administration of HPV9 vaccine and Repevax® [diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine] was investigated through Protocol 007 (n = 1,053). The objectives of this study were to assess whether concomitant administration of HPV9 vaccine and Repevax® interferes with the antibody response to any of the vaccine antigens, as well as to evaluate the safety and tolerability with co-administration of the vaccines. The non-inferiority criteria were met for all 9 HPV types ( $P < 0.001$ ), for pertussis antigens and



for seroconversion rates for all 9 HPV types, diphtheria, tetanus and polio. These findings suggest that there is no interference with the antibody response to any of the vaccine's antigens. For both vaccines, the percent of subjects with injection-site adverse events of swelling was significantly higher in the concomitant group than in the non-concomitant group (HPV9 vaccine, 13% vs 8.2%,  $P=0.01$ ; Repevax®, 39.4% vs 31.3%,  $P=0.006$ ). There were no differences between the concomitant and non-concomitant groups in erythema, temperature and pain.

## IV.9 Adverse Events of HPV9 Vaccine

HPV vaccines have been shown to be well-tolerated up to 9 years following vaccination.<sup>(28)</sup> Results of the published phase II/III study<sup>(23)</sup> (methods and design described in “IV.2 Efficacy of HPV9 Vaccine”), revealed that recipients of the HPV9 vaccine were more likely than recipients of the HPV4 vaccine to have adverse events (AEs) related to the injection site (6414/7071 participants (90.7%) vs. 6012/7078 participants [84.9%]), with the most common events being pain, swelling, erythema, and pruritus (seen in about 5-10% more subjects receiving HPV9 compared to HPV4); more than 90% of these events were mild to moderate in intensity. Serious events were defined and determined by a safety monitoring committee. The proportion of events of severe intensity was higher in the HPV9 group (233/7071 participants (3.3%) vs 183/7078 [2.6%]). Statistical significance and confidence intervals were not provided. The number of serious events that were considered vaccine-related by the reporting investigator was the same in both groups (2 participants in both groups). The frequency of systemic adverse events was generally similar in the two groups — 3948/7071 participants (55.8%) in the HPV9 vaccine group and 3883/7078 participants (54.9%) in the HPV4 vaccine group. Less than 0.1% of participants discontinued the study because of a vaccine-related adverse event (5 participants receiving HPV9 vs 3 participants receiving HPV4).

Two studies (protocols 002 and 009) presented to NACI, and a poster presentation of six integrated clinical trials focused on the safety of HPV9. Overall, results from these studies ( $n > 10,000$ ) indicated that the vaccine was well-tolerated. Most AE were injection site-related symptoms of mild or moderate intensity. The AE profile was comparable to that of HPV4 vaccine. However, an increase in mild to moderate injection-site AEs was observed. A higher proportion of girls and women (ages 9 to 26 years) experienced AEs following vaccination compared to boys (ages 9 to 12 years). There was a statistically significant difference in the incidence of injection-site swelling between girls (ages 9 to 15 years) receiving HPV9 vs HPV4. For girls and women, ages 9 to 26 years, the percent of injection-site swelling and injection-site erythema both increased following each successive dose of HPV9. The percent of injection-site pain was approximately equal across the three reporting time periods.<sup>(5)</sup>

Safety of HPV9 in prior HPV4 vaccine recipients was assessed in 900 females (protocol 006) aged 12 to 26 years who were followed for 7 months to detect potential AEs. Prior to enrolment, over 99% of subjects had received three injections of HPV4 vaccine within a one year period. The time interval between the last injection of HPV4 vaccine and the first injection of HPV9 vaccine ranged from approximately 12 to 36 months. The subjects were randomized 2:1 to HPV9 vaccine ( $n=608$ ) or saline injection (placebo group,  $n=305$ ). Five-hundred and sixty-six (93.1%) participants who received the HPV9 vaccine experienced vaccine-related AEs (3 of which discontinued the immunization), compared to 174 (57.0%) in the placebo group. The frequency of injection-site AEs was higher in the HPV9 vaccine group than in the placebo group (554/608 participants (91.1%) and 134/305 participants (43.9%), respectively). The frequencies of vaccine-related systemic AEs were comparable between the 2 groups (186/608 participants [30.6%] and 79/305 participants [25.9%], respectively). The level of significance and confidence

intervals were not provided. One participant in each exposure group experienced what was deemed by the reporting investigators (blinded to vaccine group allocation) as a serious vaccine related AE. The participant who had received the HPV9 vaccine developed tonsillitis one day after the administration of dose 1. This episode resolved after five days and the subject continued in the study and received doses 2 and 3 at the appropriate time intervals. The participant who received the saline placebo developed a common cold and sore throat after dose 2, which resolved after 4 days. The subject continued in the study and received dose 3 at the appropriate time interval. <sup>(29)</sup>

#### IV.10 Contraindications and Precautions for HPV9 Vaccine <sup>(29)</sup>

HPV9 vaccine is contraindicated in patients who are hypersensitive to any antigen in HPV4 or HPV9 vaccine, or to any ingredient in the formulation or component of the container. Individuals who develop symptoms indicative of hypersensitivity after receiving a dose of HPV9 or HPV4 vaccine should not receive further doses of any of these vaccines.

As with all injectable vaccines, appropriate medical treatment should always be readily available in case of rare anaphylactic reactions following the administration of the vaccine. Syncope (fainting) may follow any vaccination, especially in adolescents and young adults. Syncope, sometimes associated with injury when falling, has occurred after HPV vaccination. Therefore, vaccinees should be carefully observed for approximately 15 minutes after administration of all HPV vaccines.

##### Febrile Illness:

The decision to administer or delay vaccination because of a current or recent febrile illness depends largely on the severity of the symptoms and etiology. Low-grade fever itself and mild upper respiratory infection are not generally contraindications to vaccination.

##### Immunocompromised individuals:

Individuals with impaired immune responsiveness, whether due to the use of immunosuppressive therapy, a genetic defect, Human Immunodeficiency Virus (HIV) infection, or other causes, may have reduced antibody response to active immunization; however these individuals can still receive vaccine, and should be immunised with a schedule of three doses to increase the likelihood of seroconversion.

##### Pregnant Women:

Reproductive studies have been performed in female rats at a dose approximately 240 times the human dose (mg/kg basis) and have revealed no evidence of impaired female fertility or harm to the fetus due to HPV9 vaccine. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, pregnancy should be avoided during the vaccination regimen for HPV9 vaccine.

##### Nursing Women:

It is not known whether vaccine antigens are excreted in human milk. A total of 86 women were breast feeding during the vaccination period of the clinical studies for HPV9 vaccine. There were no serious adverse experiences reported in infants who were nursing during the vaccination period.

## IV.11 Other Considerations

### ***Interchangeability of HPV vaccines***

Studies using a mixed regimen of HPV vaccines were not performed for HPV9 vaccine.

Whenever possible, one brand of vaccine should be used to complete a vaccine series. If the brand of the previously received doses is not known, HPV2, HPV4, or HPV9 vaccine may be used to complete the series for genotypes 16 and 18. However, only HPV4 and HPV9 vaccines can achieve protective antibody levels against HPV types 6 and 11. In addition, HPV9 vaccine is currently the only vaccine able to provide protection against genotypes 31, 33, 45, 52, 58.

If an individual has started the series with HPV2 or HPV4 and wishes to complete the series with HPV9 vaccine, he or she should be informed that there are no interchangeability data for HPV vaccines nor are there any published data regarding two-dose HPV9 schedules. However, based on studies of HPV2 and HPV4 vaccines among adolescents, there is a theoretical basis for advising immunocompetent, non-HIV infected, individuals under 15 years of age to consider having two doses of HPV9 vaccine given 6 months apart, as this has been shown to have non-inferior immunogenicity, relative to three-dose schedules, in HPV2 and HPV4 vaccine trials among adolescents. This advice is based on expert opinion, rather than published evidence. Further data are required and NACI will review additional data on an ongoing basis.

### ***Cancer screening following HPV vaccine administration***

Routine monitoring and cervical cancer screening in women should continue to be performed as indicated, regardless of HPV vaccine administration. Recipients of HPV vaccines should not discontinue cancer screening unless recommended by a health care provider. Appropriate precautions against sexually transmitted diseases should continue to be used.

## V. RECOMMENDATIONS

As of February 5, 2015, there are three HPV vaccines authorized for use in Canada. All of these vaccines are authorized for use as a 3- dose schedule (0, 1, 6 months for HPV2 and 0, 2, and 6 months for HPV4 and HPV9). Two of these vaccines are authorized for use as a two- dose schedule (for girls 9-14 years of age with HPV2 as a t=0, 6 month schedule; and for individuals 9-13 years of age with HPV4 as a t=0, 6 or t=0, 12 month schedule). A clinical trial to assess alternate dosing schedules for HPV9 is currently underway.

NACI recommendations regarding HPV2 and HPV4 vaccines, as summarized in the Introduction of this statement, are still applicable. Please refer to the 2012 NACI Update Statement on HPV Vaccines (<http://www.phacaspc.gc.ca/publicat/ccdr-rmtc/12vol38/acs-dcc-1/index-eng.php#a5>) and 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](http://www.phac-aspc.gc.ca/naci-ccni/acs-dcc/2015/hpv-vph_0215-eng.php)) for a complete list of these recommendations. New recommendations regarding the HPV9 vaccine and minimum intervals between HPV vaccine doses in the context of existing recommendations 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/cigqci/p04-hpv-vph-eng.php>).

Please refer to Table 9 for an explanation of NACI grading of evidence.

#### Recommendation #1:

**NACI concludes that any of the currently authorized HPV vaccines in Canada can be used according to the recommended HPV immunization schedules – NACI Recommendation Evidence Grade A or B (see Table 4)**

***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 Table 4, below.*** 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. In addition, HPV9 vaccine protects against the additional five HPV types not contained in HPV4 vaccine (HPV 31, 33, 45, 52 and 58).

**Table 4. Recommended Immunization Schedule with HPV Vaccines**

RECOMMENDED GROUPS	RECOMMENDED IMMUNIZATION SCHEDULE	VACCINE(S) and NACI EVIDENCE GRADE
<b>Healthy (immunocompetent, non-HIV infected) Females 9-14 years of age (and healthy females <math>\geq 15</math> years of age in whom the first dose was administered between 9-14 years of age)</b>	2- or 3-dose schedule	HPV2 or HPV4 (Grade A)
	3-dose schedule	HPV9 (Grade B)
<b>Healthy (immunocompetent, non-HIV infected) Females <math>\geq 15</math> years of age</b>	3-dose schedule	HPV2 or HPV4 (Grade A) or HPV9 (Grade B)
<b>Healthy (immunocompetent, non-HIV infected) Males 9-14 years of age (and healthy males <math>\geq 15</math> years of age in whom the first dose was administered between 9-14 years of age)</b>	2- or 3-dose schedule	HPV4 (Grade B)
	3-dose schedule	HPV9 (Grade B)
<b>Healthy (immunocompetent, non-HIV infected) Males <math>\geq 15</math> years of age</b>	3-dose schedule	HPV4 or HPV9 (Grade B)



<b>Immunocompromised individuals and immunocompetent HIV-infected individuals</b>	3-dose schedule	HPV2, HPV4 or HPV9 in females; HPV4 or HPV9 in males  Grade I
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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 responsible for approximately 14% of anogenital cancers. HPV4 and HPV9 also protect against HPV genotypes 6 and 11, which cause over 90% of AGWs. 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 will reassess the grading of this recommendation as new evidence emerges.

#### Recommendation #2:

**NACI concludes that there is insufficient evidence at this time to recommend a 2-dose immunization schedule with HPV9 vaccine – NACI Recommendation Evidence Grade I.**

A phase III clinical trial to study the safety and immunogenicity of a 2-dose immunization schedule with HPV9 vaccine is currently under way. The goal of the 37-month study is to establish whether the investigational 2-dose regimens of 0, 6 months and 0, 12 months in boys and girls 9 to 14 years of age are safe and immunogenic, with an antibody response non-inferior to that observed in females 9 to 26 years of age who received the standard 3- dose regimen of the vaccine.

NACI will review and reassess this recommendation as new evidence emerges.

#### Recommendation #3

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

Unpublished data suggest that re-immunization with HPV9 vaccine after completion of a series with HPV4 produces lower immunogenicity to the five additional HPV genotypes (clinical significance unknown) and higher incidences of local injection site adverse events; efficacy has not been assessed.

While not recommended at a population level, individuals who have been vaccinated with HPV4 vaccine and who wish to take advantage of the additional protection provided by HPV9 vaccine may be vaccinated with HPV9 vaccine. There is insufficient evidence at this time to determine whether fewer than 3 doses of HPV9 vaccine conveys protection against the additional five HPV types in prior HPV4 vaccine recipients.



NACI will review and reassess this recommendation as new evidence emerges.

**Recommendation #4:**

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

***NACI recommends that, whenever possible, the recommended intervals between doses of HPV2 vaccine (0, 1, 6 months in a 3- dose schedule or 0 and 6 months in a 2- dose schedule), HPV4 vaccine (0, 2, 6 months in a 3- dose schedule or 0 and 6 or 12 months in a 2- dose schedule) and HPV9 vaccine (0, 2 and 6 months) should be respected.*** When an abbreviated schedule is unavoidable, the minimum intervals in a 3- dose schedule (as summarized in Figure 1) between the first and second doses of HPV vaccine is 4 weeks (1 month), the minimum interval between the second and third doses of HPV vaccine is 12 weeks (3 months), and the minimum interval between the first and third doses is 24 weeks (6 months). The minimum interval between the first and second dose in a 2- dose schedule with either HPV2 or HPV4 is 24 weeks (6 months).

## VI. 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, available at: ([http://publications.gc.ca/collections/collection\\_2014/aspc-phac/HP40-107-2014-eng.pdf](http://publications.gc.ca/collections/collection_2014/aspc-phac/HP40-107-2014-eng.pdf)).

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

1. What are effective measures to increase HPV immunization coverage?
2. What is the immunogenicity and efficacy of a 2-dose HPV9 immunization schedule compared to a 3-dose schedule?
3. What is the efficacy of the HPV9 vaccine among females 27 to 45 years and males 16 to 26 years?
4. What is the safety of HPV9 vaccine in the pregnant population?
5. What is the efficacy, immunogenicity, and safety of HPV9 vaccine among larger populations?
6. What is the efficacy, immunogenicity and safety among those receiving 1, 2 or 3 doses of HPV9 vaccine who have been previously vaccinated with the HPV4 (or HPV2) vaccine?
7. What is the efficacy and long-term immunogenicity of completing the vaccine series with HPV9 vaccine (1 or 2 doses) in individuals who have initially been vaccinated with HPV4 or HPV2 vaccine (1 or 2 doses)
8. What is the immunogenicity and efficacy of HPV9 vaccine among men having sex with men, and in other high- risk groups?

9. What is the immunogenicity and efficacy of HPV vaccines when administered at intervals shorter than the recommended intervals in the immunization schedule?

## VII. 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 enhanced surveillance in the following areas:

- Incidence and prevalence of both HPV infection and disease
- Distribution of HPV in high-risk populations (e.g. socioeconomic distribution)
- 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, 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
- Sexual behaviour
- Cervical screening behaviour

## TABLES

**Table 5. Summary of evidence (published and unpublished) related to HPV9 vaccine**

Published Study						
Evidence for efficacy						
STUDY DETAILS					SUMMARY	
Study	Vaccine	Study Design	Participants	Summary of Key Findings	Level of Evidence	Quality
Joura, E.A. et al. A 9-Valent HPV Vaccine against Infection and Intraepithelial Neoplasia in Women. <i>NEJM</i> . 2015;372:711-23. DOI: 10.1056/NEJMoa1405044 <sup>(23)</sup>	HPV9 vaccine  HPV4 vaccine	RCT Double blind, international multicentre Phase 2-3 adaptive design -control group was the group of subjects receiving quadrivalent vaccine	N= 14215 Women 16 to 26 years old	<p><u>Comparison of HPV9 and HPV4 vaccination intention-to-treat groups:</u> - the average risk reduction was 19.0 (-1.6 to 35.3) and 17.1 (-4.2 to 34.0) for High-grade cervical/vulvar/vaginal disease and High-grade cervical epithelial neoplasia/ adenocarcinoma in situ/cervical cancer respectively -risk reduction for those uninfected by HPV at day 1 and for disease related to 9 vaccine HPV types was 100 (70.4 to 100) and 100 (70.3 to 100) for High-grade cervical/vulvar/vaginal disease and High-grade cervical epithelial neoplasia/ adenocarcinoma in situ/cervical cancer respectively</p> <p><u>Comparison of HPV9 and HPV4 vaccination per-protocol efficacy groups:</u> -risk reduction for disease related to HPV-31, 33, 45, 52, and 58 was 96.7 (80.9 to 99.8) and 96.3 (79.5 to 99.8) for High-grade</p>	I	Good  -risk reduction values had very large confidence intervals

				cervical/vulvar/vaginal disease and High-grade cervical epithelial neoplasia/adenocarcinoma in situ/cervical cancer respectively -risk reduction for persistent infection greater than or equal to 6 months was 96.0 (94.4 to 97.2)		
<b>Evidence for immunogenicity</b>						
<b>STUDY DETAILS</b>					<b>SUMMARY</b>	
<b>Study</b>	<b>Vaccine</b>	<b>Study Design</b>	<b>Participants</b>	<b>Summary of Key Findings</b>	<b>Level of Evidence</b>	<b>Quality</b>
Joura, E.A. et al. A 9-Valent HPV Vaccine against Infection and Intraepithelial Neoplasia in Women. <i>NEJM</i> . 2015;372:711-23. DOI: 10.1056/NEJMoA1405044 <sup>(23)</sup>	HPV9 vaccine	RCT Double blind, international multicentre Phase 2-3 adaptive design -control group were those receiving quadrivalent vaccine  Outcome measure – GMT and seroconversion quantified with the use of a competitive Luminex immunoassay	N= 14215 Women 16 to 26 years old  -received HPV9 vaccine or HPV4 vaccine on day 1 and months 2 and 6	Antibody responses of those who received HPV9 vaccine to HPV-6, 11, 16, and 18 were non-inferior to those of the HPV4 vaccine.	I	Good  - comparison was between the per-protocol groups and not the intention-to-treat groups

Evidence for safety						
STUDY DETAILS					SUMMARY	
Study	Vaccine	Study Design	Participants	Summary of Key Findings	Level of Evidence	Quality
Joura, E.A. et al. A 9-Valent HPV Vaccine against Infection and Intraepithelial Neoplasia in Women. <i>NEJM</i> . 2015;372:711-23. DOI: 10.1056/NEJMo a1405044 <sup>(23)</sup>	HPV9 vaccine  HPV4 vaccine	RCT Double blind, international multicentre Phase 2-3 adaptive design -control group was the group of subjects receiving quadrivalent vaccine	N= 14215 Women 16 to 26 years old	- Adverse events related to injection site and of severe intensity were more common in the HPV9 group than in the HPV4 group.	I	Good

Unpublished Studies						
Evidence for immunogenicity						
DETAILS					SUMMARY	
Study	Vaccine	Study Design	Participants	Summary of Key Findings	Level of Evidence	Quality
Study 002 : Adult-Adolescent Immunobridging		Day 1, Month 2, and Month 6 Open label study: All subjects receive HPV9 vaccine  Day 1 and Month 7 Anti-HPV 6, 11,	1800 girls (9-12 years: ~1200; 13-15 years: ~600) 600 boys (9-12 years: ~400; 13-15 years: ~200) 400 young women (16-	Non-inferior immunogenicity in adolescent girls and boys vs. young women for all 9 vaccine HPV types ( $P < 0.001$ )  Supports bridging of efficacy findings in young women, 16 to 26 years of age, to girls and boys, 9 to 15 years of age	II	N/A  Pharmaceutical presentation to NACI October 2014



		16, 18, 31, 33, 45, 52, and 58 titers	26 years)			
Study 003: Women and Men immunobridging	HPV9	Day 1, Month 2, and Month 6 Open label study: All subjects receive HPV9 vaccine  Day 1 and Month 7 Anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 titers	Heterosexual men 16 to 26 years (N=1103) Women 16 to 26 years (N=1099) Men having sex with men 16 to 26 years (N=300)	The non-inferiority criterion was met for all nine HPV types (P<0.001) for heterosexual men vs women. The GMTs were lower among MSM vs heterosexual men in a 0.6 to 0.7 range which is similar to GMT ratios with HPV4 and MSM vs heterosexual men.  Seroconversion rate for MSM was >99%; GMT numbers were not reported	II	N/A  Pharmaceutical presentation to NACI February 2015
Study 009 : HPV4-to-HPV9 Immunobridging  Olsson S, Van Damme P, Herrera T, Pitisuttithum P, Block S, et al. Immunogenicity and safety of a novel 9-valent HPV L1 virus-like particle vaccine in boys and girls 9-15 years old; comparison to women 16-26	HPV9 vaccine	Randomized control trial  Double-blinded study  Day 1, Month 2, and Month 6  Day 1 and Month 7 Anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 titers  -analysis done for per-protocol	600 girls (9-12 years: ~300; 13-15 years: ~300)	-non-inferiority of the HPV9 vaccine compared to the HPV4 vaccine for HPV 6, 11, 16,18 was demonstrated by GMT ratios and seroconversion  -GMTs elicited by HPV4 vaccine for HPV 31, 33, 45, 52, 58 were 80-fold lower than GMTs in subjects receiving the HPV9 vaccine (GMT numbers were not reported) Supports bridging of efficacy findings with HPV4 vaccine to HPV9 vaccine	I	N/A  -poster presentation, presentation to NACI, product monograph

years old. International Papillomavirus Conference 2014, August 21-25, Seattle, WA. Abstract PH.PD04.03 <sup>(30)</sup>		group				
Protocol 006  Luxembourg A, Christensen S, Restrepo J, McNeil S, Kjeld- Petersen L, et al. Immunogenicity and safety of a 9-valent HPV vaccine in prior quadrivalent HPV vaccine recipients. International Papillomavirus Conference 2014, August 21-25, Seattle, WA Abstract PH.PP06.37 <sup>(31)</sup>	HPV9 vaccine	Randomized 2:1 to receive HPV9 vaccine or saline placebo  Double-blinded  Vaccine administration: Day 1, Month 2, and Month 6 study  Immunogenicity: Day 1, Month 2, and Month 7 Anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 titers  Safety: Day 1 through Month 7 Vaccination Report Card (VRC)-aided	900 girls and young women (12- 15 years: ~180; 16-26 years: ~720); all prior Gardasil recipients	- At 4 weeks post-dose 3, over 98% of subjects in the HPV9 vaccine cohort were seropositive for HPV types 31, 33, 45, 52, and 58.  -Anti-HPV 31, 33, 45, 52, and 58 GMTs were lower than in subjects administered HPV9 vaccine who were naïve to HPV4; GMT numbers were not reported  Immunogenicity provided by HPV9 for genotypes 6 and 11 was similar to HPV4 (fold difference of 0.96 and 0.98 for young girls, and 0.90 and 0.86 in the case of women), slightly higher for genotype 18 (fold difference ~ 1.05 for both groups) and lower for genotype 16 (fold difference ~ 0.80 for both groups)  Past vaccination with HPV4 did not prevent seroconversion to genotypes 31, 33, 45, 52 and 58.	I	N/A  -poster presentation, presentation to NACI, product monograph  -only assessing effects of immunogenicity among those vaccinated with HPV4; not evaluating immunogenicity compared to a non-vaccinated control group  - no confidence intervals were reported

		surveillance Serious Adverse Experiences (SAEs)				
Giuliano A, Joura E, Iversen O, Bautista O, Chen J, Moeller E, et al. Efficacy of a novel 9-valent HPV L1 vaccine against disease irrespective of HPV type. International Papillomavirus Conference 2014, August 21-25, Seattle, WA. Abstract PH.PD04.05. <sup>(32)</sup>	9vHPV vaccine  qHPV vaccine	RCT double blinded -control group receives qHPV	N=14,000 Females 16 to 26 years  -subjects were sexually active	-estimated efficacy relative to a historical placebo group  -Significant reductions in risk of CIN1 (44%), CIN2+ (63%), and condyloma (86%)  -Marginally significant reduction in risk of VIN1 or VaIN1 (52%) and nonsignificant reduction in VIN2/3 or VaIN2/3 (94.6%)  -Significant reductions in risk of Pap test abnormalities (ASCUS HR HPV positive or worse) of 44.3% and high-grade lesions (atypical squamous cells of high grade [ASC-H] or worse) of 63.8%  -Significant reductions in cervical biopsies (28%) and cervical definitive therapy (47%)	I	N/A  -poster presentation  -large confidence intervals

#### Evidence for safety

STUDY DETAILS					SUMMARY	
Study	Vaccine	Study Design	Participants	Summary of Key Findings	Level of Evidence	Quality
Study 002 : Adult-Adolescent Immunobridging		Day 1, Month 2, and Month 6 Open label study: All subjects	1800 girls (9-12 years: ~1200; 13-15 years: ~600) 600 boys (9-12 years:	2 serious adverse vaccine-related events were reported. Participation of two subjects was discontinued because of vaccine-related adverse events.	II	N/A  Pharmaceutical presentation to NACI October 2014

		receive HPV9 vaccine  Vaccination Report Card-aided surveillance  Serious Adverse Experiences	~400; 13-15 years: ~200) 400 young women (16-26 years)	Generally well tolerated in all 3 demographic groups		
Study 003: Women and Men immunobridging	HPV9	Day 1, Month 2, and Month 6 Open label study: All subjects receive HPV9 vaccine  Vaccination Report Card-aided surveillance  Serious Adverse Experiences	Heterosexual men (N=1103) Women (N=1099) Men having sex with men (N=300)	The percentage of all vaccine-related adverse events was lower among men (70.9%) than among women (86%). There were no serious adverse events or deaths.	II	N/A  Pharmaceutical presentation to NACI February 2015  The level of significance and confidence intervals were not provided.
Study 009 : HPV4-to-HPV9 Immunobridging		Randomized control trial	600 girls (9-12 years: ~300; 13-15 years: ~300)	No statistically significant differences in the incidence of injection-site erythema and injection-site pain between subjects receiving HPV9 vs	I	N/A  -poster presentation,

Olsson S, Van Damme P, Herrera T, Pitisuttithum P, Block S, et al. Immunogenicity and safety of a novel 9-valent HPV L1 virus-like particle vaccine in boys and girls 9-15 years old; comparison to women 16-26 years old. International Papillomavirus Conference 2014, August 21-25, Seattle, WA. Abstract PH.PD04.03. <sup>(30)</sup>		Double-blinded study  Day 1, Month 2, and Month 6  Day 1 through Month 7 Vaccination Report Card (VRC)-aided surveillance of Serious Adverse Experiences (SAEs)  -control group subjects were those receiving HPV4		HPV4  There was a statistically significant difference in the incidence of injection-site swelling between subjects receiving HPV9 vs HPV4 %Risk difference was 11.8 (CI 3.9; 19.6, p=0.003)  Most injection-site reactions were of mild or moderate intensity		presentation to NACI, product monograph
Protocol 006  Luxembourg A, Christensen S, Restrepo J, McNeil S, Kjeld-Petersen L, et al.	HPV9 vaccine	Randomized 2:1 to receive HPV9 vaccine or saline placebo	900 girls and young women (12-15 years: ~180; 16-26 years: ~720); all prior HPV4	-frequency of vaccine-related AEs was higher in the HPV9 vaccine group than in the placebo group (93.1% and 57.0% respectively)  -frequency of injection-site AEs was higher in the HPV9 vaccine group than in the placebo group (91.1%)	I	N/A  -poster presentation, presentation to NACI, product monograph



Immunogenicity and safety of a 9-valent HPV vaccine in prior quadrivalent HPV vaccine recipients. International Papillomavirus Conference 2014, August 21-25, Seattle, WA Abstract PH.PP06.37 <sup>(31)</sup>		<p>Double-blinded</p> <p>Vaccine administration: Day 1, Month 2, and Month 6 study</p> <p>Immunogenicity: Day 1, Month 2, and Month 7 Anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 titers</p> <p>Safety: Day 1 through Month 7 Vaccination Report Card (VRC)-aided surveillance Serious Adverse Experiences (SAEs)</p>	vaccine recipients	<p>and 43.9%, respectively).</p> <p>-frequencies of vaccine-related systemic AEs were comparable between the 2 groups (30.6% and 25.9%, respectively)</p> <p>-one serious AE was determined to be related to HPV9 vaccine. A similar proportion of the placebo group has also experienced a systemic AE (25.9%).</p> <p>HPV9 vaccine has an acceptable safety profile in prior HPV4 vaccine recipients</p> <p>– Most injection-site reactions are of mild or moderate intensity</p>		- no confidence intervals were reported
Moreira E, Joura E, Van Damme P, Schilling A, Kosalaraska P,	HPV9 vaccine	Integrated summary of 6 clinical trials	<p>N = 13,307</p> <p>Females 9 to 26 years old</p> <p>Males 9 to 15</p>	<p>-analyses on “all subjects as treated” population</p> <p>92.2% of subjects who received the HPV9 vaccine reported an AE</p>	I	<p>N/A</p> <p>-poster presentation results only</p>

et al. Safety and tolerability of a novel 9-valent HPV vaccine. International Papillomavirus Conference 2014, August 21-25, Seattle, WA Abstract PH.PP06.39 <sup>(33)</sup>		4/5 were randomized and had control group	years old	<p>Most adverse experiences were injection-site AEs (88.3%) and were mild to moderate intensity.</p> <p>Two studies report that HPV9 vaccine has an AE profile comparable to that of the HPV4 vaccine except for a higher incidence of injection-site AEs (no statistical analysis done)</p> <p>No deaths</p>		<p>-no confidence intervals were reported</p> <p>-no analysis of differences to determine statistical significance</p>
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#### Unpublished Studies

#### Evidence for simultaneous administration with other vaccines

STUDY DETAILS					SUMMARY	
Study	Vaccine	Study Design	Participants	Summary of Key Findings	Level of Evidence	Quality
<p>Protocol 005</p> <p>Schilling A, Parra M, Gutierrez M, Restrepo J, et al.</p> <p>Immunogenicity and tolerability of a novel 9-valent HPV vaccine given</p>	<p>HPV9</p> <p>Menactra</p> <p>Adacel</p>	<p>-participants received HPV9 Day 1, and at Months 2 and 6, and Menactra and Adacel either on Day 1 or at Month 1</p> <p>Serology</p>	<p>N=1237</p> <p>Males and females 11 to 15 years old</p>	<p>Non-inferiority criteria were met for concomitant vs non-concomitant vaccination for all 9 HPV types, <i>N. meningitides</i> serogroups, antipertussis responses and diphtheria and tetanus titers</p> <p>The authors report that the AE profile was generally comparable between the concomitant and non-concomitant groups. There were no vaccine-related serious AEs.</p>	I	<p>N/A</p> <p>-poster presentation, presentation to NACI, product monograph</p> <p>-for AE, no confidence intervals and no analysis was done to determine</p>

concomitantly with Menactra and Adacel in 11 to 15 year old boys & girls. International Papillomavirus Conference 2014, August 21-25, Seattle, WA. Abstract PH.PD04.04 <sup>(11)</sup> )		<p>testing done at day 1, month 1, 2, 6, 7</p> <p>Open label</p> <p>Comparison between concomitant group (receiving vaccines at the same time) and non-concomitant group (receiving vaccines at different times)</p> <p>Outcome measures; -Anti-HPV6/11/16/18/31/33/45/52/58 titers - Antibodies</p>				statistical significance
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		to Menactra and Adacel antigens				
Protocol 007  Kosalaraksa P, Mehlsen J, Vesikari T, Forstén A, Helm K, et al. An open-label, randomized study of a nine-valent human papillomavirus vaccine given concomitantly with Repevax in healthy adolescents aged 11-15 years. International Papillomavirus Conference 2014, August 21-25, Seattle, WA Abstract PH.PP06.30. <sup>(1)</sup>	HPV9 vaccine Repevax	-participants received HPV9 Day 1, and at Months 2 and 6, and Repevax either on Day 1 or at Month 1  Serology testing done at day 1, month 1, 2, 6, 7  RCT Open label multicentre -control group is non- concomitant group not receiving	males (n=526)  females (n=528) aged 11 to 15 years	Non-inferiority criteria were met for concomitant vs non-concomitant vaccination for: -Anti-HPV6, 11, 16, 18, 31, 33, 45, 52, 58 GMTs at 4 weeks post-dose 3 -Percentage of subjects who seroconverted to Anti-HPV6, 11, 16, 18, 31, 33, 45, 52, 58 by 4 weeks post-dose 3 -Seroconversion rates for diphtheria, tetanus, and poliovirus Types 1, 2, and 3 at 4 weeks postvaccination with Repevax -All 4 pertussis antigen GMTs (anti- pertussis toxin [PT], anti-pertussis filamentous hemagglutinin [FHA], anti-pertussis pertactin [PRN], and antipertussis fimbriae 2/3 [FIM]), at 4 weeks post-vaccination with Repevax  -No deaths -No discontinuations in either group due to an AE -For both vaccines, the % of subjects with injection-site AEs of	I	N/A  - poster presentation, presentation to NACI, product monograph  -only assessing effects of immunogenicity if given concomitantly; not evaluating immunogenicity compared to a non- vaccinated control group

3)		<p>vaccines at the same time</p> <p>Outcome measures;</p> <ul style="list-style-type: none"> <li>-Anti-HPV6/11/16/18/31/33/45/52/58 titers</li> <li>- Antibodies to Repevax antigens</li> </ul>		<p>swelling (Day 1-5) was significantly higher in the concomitant group than in the non-concomitant group (HPV9 vaccine, 13% vs 8.2%, <math>P=0.01</math>; Repevax, 39.4% vs 31.3%, <math>P=0.006</math>).</p> <p>No difference shown for erythema, temperature and pain</p>		
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**Table 6. Summary of evidence related to minimum intervals between vaccine doses**

STUDY DETAILS						SUMMARY	
Study	Vaccine	Study Design	Participants	Dosage Schedule	Summary of Relevant Findings	Level of Evidence	Quality
Cervarix Data on File. Study 580299/008. 2011. Data accessed through GSK Clinical Register accessible at <a href="http://www.gsk-clinicalstudyregister.com/">http://www.gsk-clinicalstudyregister.com/</a>	Cervarix (bivalent)	Post-hoc analysis of double-blind, randomize, controlled Phase III clinical study	18, 644 females aged 15-25	0, 1, 6 months (n=1043)  Dose 1-3 = 150± 15 days (5 months) (n=215-238)  0, 2, 6 months (n=61-70) Dose 2-3 = 4 months	Post-hoc analysis of data suggests similar Ab titres 1 month after dose 3 with alternate schedules.	I	Fair (statistical analysis not provided)
Hillman, RJ <i>et al.</i> , 2012, Clinical and Vaccine Immunology <sup>(34)</sup>  protocol 020; NCT00090285 <sup>(5)</sup>	Gardasil (quadrivalent)	Randomized, placebo-controlled, double-blind immunogenicity study	4, 065 males aged 16-26	0, 2 months (± 3 weeks), 6 months (± 4 weeks) 'flexibility' range	Vaccine was highly immunogenic in males for HPV 6, 11, 16, 18, similar results to female studies.	I	Fair (results were not stratified to allow comparison of different dosing schedules)
Giuliano, AR <i>et al.</i> , 2011, NEJM, <sup>(32)</sup>	Gardasil (quadrivalent)	Randomized, placebo-controlled,	4, 065 males aged 16-26	0, 2 months (± 3 weeks), 6 months (± 4 weeks)	Vaccine effective against external anogenital lesions (associated with	I	Fair (results were not stratified to allow comparison of different dosing

		double-blind study		'flexibility' range	HPV 6, 11, 16, or 18) in men up to 30 months post-vaccine.		schedules)
Palefsky, JM <i>et al.</i> , 2011, NEJM <sup>(35)</sup>	Gardasil (quadrivalent)	Randomized, placebo-controlled, double-blind study	602 MSM aged 16-26	0, 2 months ( $\pm$ 3 weeks), 6 months ( $\pm$ 4 weeks) 'flexibility' range	Vaccination reduced rates of anal intraepithelial neoplasia (resulting from HPV 6, 11, 16, or 18) in MSM up to 36 months post vaccination.	I	Fair (results were not stratified to allow comparison of different dosing schedules)
Draper, E <i>et al.</i> , 2013, PLOS ONE <sup>(27)</sup>	Gardasil <sup>®</sup> (quadrivalent) versus Cervarix <sup>®</sup> (bivalent)	Phase IV randomized, observer-blinded immunogenicity study	198 females aged 12-15 (Cervarix <sup>®</sup> n=96 Gardasil <sup>®</sup> n=102)	0, 1, 6 months (Cervarix <sup>®</sup> n=96)  0, 1, 6 (Gardasil <sup>®</sup> n=102) 'flexibility' range	Gardasil <sup>®</sup> and Cervarix <sup>®</sup> both elicited cross-neutralizing antibodies against non-vaccine HPV types in serum and genital secretions. Both vaccines elicited high titers of neutralizing antibodies against HPV 16 and 18. Response magnitude greater with Cervarix <sup>®</sup> compared to Gardasil <sup>®</sup> at 1 and 6 months after last dose.	I (no control group)	Fair (No unimmunized control group or group with standard schedule for comparison)
Crowe, E <i>et al.</i> , 2014, BMJ <sup>(36)</sup>	Gardasil (quadrivalent)	Case-control analysis of	128039 females aged 12-26 in	1-2 = 1 month	- 117/128039 (0.108%) subjects excluded due to	II-2	Fair (descriptive only, no assessment of

		linked administra- tive health datasets	Queensland, Australia (2007-2011)	2-3 = 3 months  1-3 = 4 months	breach of minimum 1-3 interval - 1569/128039 (1.225%) subjects excluded due to breach of minimum 2-3 interval - 246/128039 (0.192%) subjects excluded due to breach of minimum 1-2 interval		immunogenicity, safety, efficacy)
Sandri, KJ <i>et al.</i> , 2014, PLOS ONE <sup>(37)</sup>	Gardasil (quadrivalent)	Retrospec- tive study	1259 Females aged 10-26 (2006-2009) in USA accessing 'Safety Net Healthcare' (low-income, uninsured, vulnerable populations) (2007-2010)	1-2 = 1 month  2-3 = 3 months  1-3 = 6 months	- 14.2% 'early' dosing (n=49) among 3-dose populations  (timing of 'early' dose not provided)	II-3	Fair (descriptive only, no assessment of immunogenicity, safety, efficacy)
Harper, DM <i>et al.</i> , 2013, PLOS ONE <sup>(24)</sup>	Gardasil (quadrivalent)	Retrospec- tive study	2993 Females aged 10-26 in USA accessing 'Safety Net Healthcare' (low-income, uninsured, vulnerable populations) (2007-2010)	1-2 = 4weeks 2-3 = 12weeks 1-3 = 24weeks (6 months)	- <1% had 'early' dose interval 1-2 (n=2) - 2% had 'early' dose interval 2-3 (n=27) - 4% had 'early' dose interval 1-3 (n=56) - Early interval 1-3 was significantly more frequent than	II-2	Fair (descriptive only, no assessment of immunogenicity, safety, efficacy)

			(n=1464 receiving 3 doses)		other early intervals		
Dorell, CG <i>et al.</i> , 2012, Vaccine <sup>(25)</sup>	Gardasil (quadrivalent) and Cervarix (bivalent)	Survey (National Immunization Survey – Teen)	7549 females aged 13-17 in USA (2008-2009)	0, 1-2 months, 6-7 months (24 weeks)	- 0.1% (0.0-0.3) had ‘early’ dose interval 1-2 among girls receiving min 2 doses (n=6091) - 2.5% (1.9-3.4) had ‘early’ dose interval 2-3 among girls receiving min 3 doses (n=4369) - 4.8% (3.8-5.9) had ‘early’ dose interval 1-3 among girls receiving min 3 doses (n=4369)  (extent of ‘early’ dose and vaccine type not provided)	II-3 (relied on accuracy of parental information)	Fair (descriptive only, no assessment of immunogenicity, safety, efficacy)
Rubin, RF <i>et al.</i> , 2012, J Community Health <sup>(38)</sup>	Gardasil (quadrivalent)	Retrospective chart review	10821 Females aged 9-26 (2006-2010) in USA from one private practice	1-2 = 4 weeks 2-3 = 80 days 1-3 = <i>Not specified</i>	- 0.7% ‘early’ dose 3 (n=30) - 0.1% ‘early’ dose 2 (n=4)  (dose intervals not clearly defined)	II-3	Fair (descriptive only, no assessment of immunogenicity, safety, efficacy)
Widdice, LE <i>et al.</i> , 2011, Pediatrics <sup>(26)</sup>	Gardasil (quadrivalent)	Retrospective study	3297 Females aged 9-26 in USA (2006-2008)	1-2 = 4 weeks among females receiving at least 2	- 0.0% had ‘early’ dose interval 1-2 (n=0) - 1.8% had ‘early’ dose interval 2-3 (n=25) among girls	II-2	Fair (descriptive only, no assessment of immunogenicity, safety, efficacy)

				<p>doses 2-3 = 12weeks among girls receiving 3 doses (n=1477)</p> <p>1-3 = 24weeks (6 months) among girls receiving 3 doses (n=1477)</p>	<p>receiving 3 doses (n=1477) - 2.3% had 'early' dose interval 1-3 (n=33)</p>		
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**Table 7. 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 8. 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 9. NACI Recommendation for Immunization -- Grades**

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

## LIST OF ABBREVIATIONS

<b>Abbreviation</b>	<b>Term</b>
AE	Adverse events
AEFI	Adverse Events Following Immunization
AGW	Anogenital warts
AIN	Anal intraepithelial neoplasia
AIS	Adenocarcinoma in situ
CENTRAL	Cochrane Central Registry of Controlled Trials
CFV	Swiss Federal Vaccination Committee
CIN	Cervical intraepithelial neoplasia
CIQ	Comité sur l'immunisation du Québec
cLIA	competitive Luminex immunoassay
EMA	European Medicines Agency
GMC	Geometric mean concentration
GMT	Geometric Mean Titre
GMR	Geometric Mean Ratio
GSK	GlaxoSmithKline
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)
HPVWG	Human Papillomavirus Working Group
JCVI	Joint Committee on Vaccination and Immunisation
MSM	Men having sex with men
NACI	National Advisory Committee on Immunization
OFSP	Swiss Federal Public Health Office
RCT	Randomized control trial
SAGE	Strategic Advisory Group of Experts
The Agency	Public Health Agency of Canada
µg	Microgram
VIN	Vulvar intraepithelial neoplasia
VaIN	Vaginal intraepithelial neoplasia
WHO	World Health Organization

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