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

Update on the recommended Human Papillomavirus (HPV) vaccine immunization schedule

PROTECTING CANADIANS FROM ILLNESS

Public Health Agency of Canada
Agence de la santé publique du Canada

Canada

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— Public Health Agency of Canada

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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 table 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 16 and 18 and others 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. Low-risk HPV types can cause anogenital warts (AGW). Most cases (>90%) of AGW are attributable to HPV types 6 and 11. Gardasil® (HPV4 vaccine) has been authorized for use in Canada since 2006 for the prevention of infection caused by HPV types 6, 11, 16 and 18 -related cancers and genital warts. 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.
2. Who	Gardasil® or Cervarix® are recommended for the prevention of cervical cancer and adenocarcinoma *in situ* (AIS) in: • females 9 through 26 years of age ➢ females 15 through 26 years of age who have had previous Pap test abnormalities, including cervical cancer and external genital warts Gardasil® is recommended for the prevention of vulvar, vaginal, anal cancers and their precursors, and AGW in: • females 9 through 26 years of age Gardasil® is recommended for the prevention of anal intraepithelial neoplasia (AIN), anal cancer, and AGW in: • males between 9 and 26 years of age, including males who have sex with males • Cervarix® is not recommended for males at this time Gardasil® or Cervarix® may be administered to: • females over 26 years of age Gardasil® may be administered to: • males over 26 years of age HPV vaccines are not recommended for: • females or males < 9 years of age as no immunogenicity or efficacy data are available in these groups

3. How	HPV vaccines have been licensed to be given as three separate 0.5 mL doses: HPV2 vaccine at months 0, 1, and 6 and HPV4 vaccine at months 0, 2, and 6. As of July 3, 2014, HPV2 vaccine has also 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).[1] New evidence on a 2- vs 3-dose HPV immunization schedule has recently been summarized and reviewed by other immunization technical advisory groups, including the World Health Organization's Strategic Advisory Group of Experts (WHO's SAGE). Consistent with recommendations by these groups, NACI now recommends that HPV2 and HPV4 vaccines may be administered to immunocompetent individuals 9-14 years of age as two separate 0.5 mL doses at months 0 and 6-12. Immunocompromised and 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. 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. Women must consult with their health care professional for regular cervical cancer screening (i.e. Pap tests) regardless of HPV vaccination status. 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.

I. INTRODUCTION

The purpose of this statement is to determine the optimal HPV immunization schedule in groups for whom HPV vaccine is recommended in Canada, and to summarize the evidence reviewed by other immunization technical advisory groups, including the World Health Organization's (WHO's) Strategic Advisory Group of Experts (SAGE) on immunization, on the effect of a 2-dose HPV vaccine schedule, compared with the 3-dose schedule authorized for use of both bivalent (Cervarix® [HPV2]) and quadrivalent (Gardasil® [HPV4]) HPV vaccines. As of May 2013, Cervarix® has been authorized for use in females 9-45 years of age (expanded from 10-26 years of age). On July 3, 2014, Cervarix® was authorized for use in Canada as a 2-dose schedule (0, 6 months) in girls 9 to 14 years of age at the time of first injection.

This statement will:

- Provide an overview of previous NACI recommendations for HPV immunization
- Outline the national goal for HPV immunization, and current status of HPV immunization programs in Canada
- Summarize the evidence reviewed and evidence-based recommendations made by other immunization technical advisory groups that informed the development of this statement
- Provide recommendations for the optimal HPV immunization schedule in Canada

Clinical studies of two HPV vaccines authorized for use in Canada demonstrate that both vaccines are generally well tolerated, immunogenic and efficacious using a 3-dose schedule. Authorization for girls 9 to 15 years has been provided on the basis of immunogenicity evidence and immunobridging data to older females.[2] In randomized control trials (RCTs) involving older children and adolescents, antibody concentrations following immunization have been observed to be inversely correlated with age, with higher antibody levels demonstrated in individuals between 9 to 15 years of age, compared to those 16 years and older.[3]-[7]

In Canada, the National Advisory Committee on Immunization (NACI)[2][8] 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. Either HPV2 or HPV4 vaccine is recommended for the prevention of cervical cancer and its precursors in females, including those who have had previous Pap test abnormalities, cervical cancer or anogenital warts (AGW). HPV4 vaccine is also recommended for the prevention of vulvar, vaginal, and anal cancers and their precursors, and AGW in females, as well as anogenital cancer and AGW in males. In its 2012 Advisory Committee Statement, NACI recommended a 3-dose HPV immunization schedule 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 use of HPV Vaccine (2012)[2]

RECOMMENDED GROUPS	NACI RECOMMENDATION GRADE BASED ON EVIDENCE AVAILABLE (see Table 7 for Grading descriptions)
Females 9-26 years of age	Grade A for Gardasil® or Cervarix®
Females 14-26 years of age with previous Pap abnormalities or AGW	Grade B for Gardasil® or Cervarix®
Females >26 years of age	Grade A for Gardasil®; Grade B for Cervarix®
Males 9-26 years of age for the prevention of anal AIN) grades 1, 2, and 3, anal cancer, and AGW	Grade A for Gardasil®
Males 9-26 years of age for the prevention of penile, perianal and perineal intraepithelial neoplasias and associated cancers	Grade B for Gardasil®
Males who have sex with males ≥ 9 years of age	Grade A for Gardasil®
Immunocompromised: either vaccine can be administered, however the immunogenicity and efficacy has not been fully determined in this population and thus individuals may not derive benefit from these vaccines	Grade I

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.[9] This goal was expanded in 2014 to include the HPV-related burden of disease from conditions other than cancer, and the entire population rather than just females. The current national HPV immunization goal is to reduce vaccine preventable HPV related morbidity and mortality in the Canadian population.[10]

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). Twelve of thirteen jurisdictions are currently offering a 3-dose HPV immunization schedule. In 2007, the *Comité sur l'immunisation du Québec* (*CIQ*) recommended an extended schedule for HPV immunization starting in grade 4 at 0 and 6 months with a third dose at 60 months if deemed necessary. This program was implemented in 2008.[11] Since 2013, Quebec has been implementing a 2-dose vaccine schedule with an interval of at least 6 months between doses for girls in grade 4.[12] In 2010, British Columbia changed their 3-dose HPV program that was offered in grade 6 to an extended dose schedule with 2 doses given 6 months apart in grade 6 and a planned third dose to be given 60 months after the first; the third dose was reintroduced 36 months after the first in grade 9 in September 2013.[13]

In 2012, Switzerland's[14]-[16] committee of immunization experts (Swiss Federal Vaccination Committee [CFV] and the Swiss Federal Public Health Office [OFSP]) recommended 2 doses of HPV vaccine at an interval of 4 to 6 months for girls 11 to 14 years of age. In April 2014, the Who's SAGE[16][17] recommended a 2-dose HPV vaccination schedule with an interval of at least 6 months between the first and second dose for girls aged less than 15 years and girls 15 years of age and older when the first dose was received before 15 years of age. In March 2014, the United Kingdom's Joint Committee on Vaccination and Immunisation (JCVI)[18] recommended a 2-dose vaccination schedule with an interval of 6 to 24 months between doses for girls who received their priming dose at less than 15 years of age.[19] By April 2014, a 2-dose (0, 6 months) schedule for HPV2 among girls 9 to 14 years of age and HPV4 among 9 to 13 year old girls and boys was approved by the European Medicines Agency (EMA).[16][20] With the EMA, WHO, and GAVI, the Vaccine Alliance, endorsing a 2-dose HPV immunization schedule and manufacturers receiving approval for a 2-dose schedule in many jurisdictions, there has been rapid global adoption of 2-dose programs for both licensed HPV vaccines.

II. METHODS

At the NACI meeting held on June 5, 2014, NACI reviewed the SAGE methodology for the development of vaccine position papers[21], as well as the evidence used by the SAGE HPV working group (WG) for the development of the recommended 2-dose HPV immunization schedule for immunocompetent girls 9-14 years of age.[22] It was determined that the systematic literature review used by SAGE meets the NACI criteria in terms of the quality of process and standards used for knowledge retrieval and synthesis. Similarly, additional evidence reviewed by the SAGE HPV WG (including studies and presentations relevant to Canada) and the considered topics and outcomes were believed to be applicable for the purpose of NACI's HPV WG's Statement development. It was also determined that any additional review conducted by NACI during the time period covered in the systematic review of literature on alternative vaccination schedules conducted for the SAGE HPV WG (from the earliest publication date of PubMed, the Cochrane Central Registry of Controlled Trials (CENTRAL) and trials registered to the last week of January 2014) would not be productive, and therefore it was suggested that additional literature searches conducted by the NACI HPV WG should include only studies not included in the SAGE report, and that the time period for the search should be extended.

SAGE's terms of reference and methodology[23][24] for recommendation development have been previously published. Evidence for developing recommendations for a 2-dose HPV immunization schedule by SAGE was obtained through[22]:

- The Ad hoc Expert Consultation on Human Papilloma Virus Vaccine schedules held in Geneva, November 18, 2013. Information provided at the meeting included unpublished or confidential information from clinical trials of both licensed vaccines.
- The systematic review of published and grey literature[1] on randomized comparisons between girls (or women) of the same age and non-randomized comparisons between girls receiving 2 doses and girls or women receiving 3 doses.
- A review of the data from observational studies.

[1]Grey literature publications are non-conventional, fugitive, and sometimes ephemeral publications. They may include, but are not limited to the following types of materials: reports (pre-prints, preliminary progress and advanced reports, technical reports, statistical reports, memoranda, state-of-the art reports, market research reports, etc.), theses, conference proceedings, technical specifications and standards, non-commercial translations, bibliographies, technical and commercial documentation, and official documents not published commercially (primarily government reports and documents). (http://www.greylit.org/about)

- A review of information provided to the EMA for the approval of the administration of HPV vaccine according to an alternative 2-dose schedule.

SAGE reviewed the effects of 2- and 3-dose schedules of HPV2 and HPV4 vaccine on immunological (including, but not limited to geometric mean [antibody] concentration [GMC], seropositivity, seroconversion, avidity) and clinical (including, but not limited to CIN3+, CIN2+, AGW, incident infection) outcomes in adolescent girls. RCTs and non-randomized prospective controlled trials published up to January 2014 were systematically reviewed for 3 different comparisons:

- Comparisons of schedules with different numbers of doses (2 doses vs. 3 doses of the same vaccine and the same dosage)
- Comparison of schedules with same numbers of doses (2 doses vs. 2 doses of the same vaccine)
    - different intervals, same dosage
    - same intervals, different dosage

The NACI HPV WG reviewed key issues concerning currently recommended immunization schedules with the HPV2 and HPV4 vaccines approved for use in Canada, with particular consideration given to immunogenicity, effectiveness and efficacy of the administration of a 2-dose schedule in healthy individuals. Building on the previously published reviews conducted by SAGE and the EMA, a further literature search and review of articles published over the last five years (May 12, 2009 to May 12, 2014), and limited to the English language was completed. To identify studies evaluating the efficacy and immunogenicity of HPV2 and HPV4 vaccines using the 2-dose schedule, a systematic search of Medline, CINAHL, EMBASE, Google Scholar and NHS Evidence was conducted. Keywords included: papillomavirus vaccines, HPV vaccine, 2-dose, 3-dose, bivalent, trivalent and variations thereof. A total of 20 full text articles were identified and reviewed. Editorial articles, review articles, and articles already included in the WHO SAGE *Evidence-based recommendations on Human Papilloma Virus (HPV) Vaccines Schedules: Background paper for SAGE discussions* were excluded. In addition, two studies mentioned the 2-dose schedule but did not evaluate efficacy or immunogenicity: one was an economic evaluation and was excluded; the other reported on effectiveness rather than efficacy and was retained as supplemental information. Two publications reported on immunogenicity and were retained for the purpose of this Advisory Committee Statement. The three retained studies are included in the summary of evidence table (Table 4), and are discussed in the text.

The knowledge synthesis was performed by two medical advisors at the Agency and a Public Health and Preventive Medicine resident, and supervised by the HPV WG. The HPV WG Chair and Agency medical advisors presented the evidence and proposed recommendations to NACI on September 5, 2014. Following a thorough review of the evidence and consultation at the NACI meeting of October 1, 2014, the committee voted on specific recommendations. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described below.

III. EPIDEMIOLOGY

HPV is not a reportable disease in any jurisdiction in Canada. The epidemiology of HPV in Canada has previously been published in the *Update on Human Papillomavirus (HPV) Vaccines* (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/12vol38/acs-dcc-1/index-eng.php) released in

January 2012. For information on symptoms and natural progression of disease, please refer to the *Canadian Immunizaton Guide* (CIG) (http://www.phac-aspc.gc.ca/publicat/cig-gci/).

IV. VACCINE

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

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

Brand name	CERVARIX® (HPV2)	GARDASIL® (HPV4)
Immunogens	recombinant L1 proteins from HPV types16 and18	recombinant L1 protein of HPV Types 6, 11, 16, and 18
Manufacturer	GlaxoSmithKline Inc.	Merck Canada Inc.
Authorization	• females 9 through 45 years of age[2]	• females 9 to 45 years of age • males 9 through 26 years of age
Antigen Components (µg):		
HPV type 18 L1 protein	20	20
HPV type 16 L1 protein	20	40
HPV type 11 L1 protein		40
HPV type 6 L1 protein		20
Other ingredients	3-0-desacyl-4'-monophosphoryl lipid A and aluminum hydroxide (AS04,adjuvant), sodium chloride, sodium dihydrogen phosphate dihydrate, water for injection	aluminum hydroxyphosphate sulfate (adjuvant), sodium chloride, L-histidine, polysorbate 80, sodium borate, water for injection

[2] As of May 2013, Cervarix® has been authorized for use in females 9-45 years of age (expanded from 10-26 years of age).

IV.1a Efficacy

HPV vaccines have been authorized for use based on the demonstration of their clinical efficacy in females 15 to 45 years of age and males 16 to 26 years of age. In younger individuals, efficacy has been inferred using pre-licensure immunobridging studies that have demonstrated non-inferiority in antibody response to the vaccines' antigens among different age groups. The underlying premise of immunogenicity bridging studies is that if the trial population attains similar antibody levels as the population in which efficacy is already established, efficacy results can be inferred in the new population. Detailed information on the efficacy and immunogenicity data from bridging studies using a three-dose schedule that was previously reviewed by NACI is available in the *NACI Update on Human Papillomavirus (HPV)* (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/12vol38/acs-dcc-1/index-eng.php).

Efficacy data for younger age groups that were available through non-randomized comparisons of clinical outcomes in females partially vaccinated [(25)-(29)] with HPV2, as well as limited data[(30)-(32)] that were presented from one unpublished RCT in India on incident infections following immunization with HPV4 vaccine was reviewed by SAGE. Data on non-randomized comparisons were obtained from GSK's HPV-008 and HPV-009 trials for Cervarix® provided to the EMA.

HPV-008 was a phase III, double-blind, randomized, and controlled multi-centre efficacy study of HPV2 in over 18,665 healthy women 15-25 years of age in multiple regions of the world (North America, Latin America, Europe, Australia and Asia). A total of 258 females, 15-25 years of age, who had received only 2 doses were evaluated for efficacy against incident infection, and 235 females who had received 2 doses were evaluated for efficacy against 6-month persistent infection. At month 48, vaccine efficacy against incident infection was 84.5% [31.7, 98.3], while vaccine efficacy against 6-month persistent infection was 100% [33.1, 100]. HPV-009 was a phase III, double-blind, randomized, controlled study designed to evaluate the efficacy, safety and immunogenicity of HPV2 vaccine in 7,466 healthy women aged 18 to 25 years in Costa Rica. Vaccine efficacy against 12-month persistent infection was evaluated in 802 females who either received 2 doses of HPV2 (n=422) or Hepatitis A (control, n=380) vaccine. HPV2 vaccine efficacy was estimated to be 84.1% [50.2, 96.3], with an estimated efficacy relative to the 3-dose regimen of 104% [69.3, 129].

SAGE also reviewed limited data on clinical outcomes following immunization with HPV4 vaccine from a RCT in India, in which incident infections were more common in girls 10 to 18 years of age who received a 2-dose schedule (6/36 incident infections, 17%) compared to the 3-dose group (1/44 incident infections, 2%). However, methods have not been published and information from this trial was only available from the Ad hoc Expert Consultation meeting and one conference abstract.[(31)]

No further studies on vaccine efficacy have been published since the SAGE review.

IV.1b Effectiveness

One study not included in the SAGE review, identified through the supplementary literature search conducted to inform this advisory committee statement, sought to determine the effect of introducing the HPV vaccine on the prevalence of cervical dysplasia in adolescent girls undergoing routine reproductive health care. The findings are summarized in Table 4. The authors reviewed the records of all girls who received Pap tests at an adolescent clinic

associated with an American, urban academic medical centre between January 2006 and September 2009. Two hundred seventeen girls aged 11 to 20 years underwent a total of 488 Pap tests. Significantly more girls (42%) with no vaccine had at least one abnormal Pap test, compared to 14% of girls with at least one dose of HPV vaccine (p = 0.002). The odds ratio of having at least one abnormal Pap test for the vaccinated group was 0.254 (CI = 0.093-0.698; p = 0.008). The authors state that those with at least one dose of HPV vaccine prior to first Pap test were less likely to have abnormal results than those with no vaccine, suggesting that HPV vaccination may reduce the risk of developing cervical dysplasia. No comparison was done between one, two or three doses; however, this study suggests that those with even one dose of vaccine may be less likely to have abnormal Pap test results compared to those who are not vaccinated.

IV.2 Immunogenicity

Females

SAGE reviewed immunogenicity data from trials in girls and women that compared 2-dose and 3-dose schedules for both vaccines authorized in Canada. The results extracted from RCTs were analysed and presented according to the income status of countries in which the trials were conducted (high versus middle and low income).

SAGE reviewed results from three RCTs in girls, two of which were conducted in high income countries (Canada and Germany).

A study conducted only in Canada[(6)(33)] was a randomized, phase III post-licensure immunogenicity trial that enrolled 520 girls 9 to 13 years of age allocated to a 2-dose (0, 6 month) or 3-dose (0, 2, 6 month) schedule using HPV4 vaccine. Detailed results from this study were reported by Dobson et al. and Krajden, et al; this study also included a 3-dose arm in young women aged 16-26 years, described below. A study conducted in Canada and Germany (HPV-048)[(3)(34)-(36)] was a phase I/II randomized trial that assessed the immunogenicity of HPV2 vaccine when administered to 479 girls 9 to 14 years of age according to a 2-dose (0, 6 months) or standard dosing schedule (0, 1, 6 months).

An analysis of the GMC reported by these studies showed inconsistent results for HPV16. Non-inferiority of a 2-dose compared to a 3-dose schedule was demonstrated in the study that was conducted only in Canada, while the results from HPV-048 were inconclusive. For HPV18, SAGE found the GMC results from both trials to be consistent, with values in the 2-dose group being non-inferior compared to the 3-dose group (weighted mean difference corresponding to a GMC ratio of 0.72, 95% CI 0.62, 0.84). Further evaluation of immunogenicity on the basis of seroconversion rates, demonstrated non-inferiority of a 2-dose schedule at all time points (up to 36 months) for HPV16 in both trials and for HPV18 in HPV-048 study when the non-inferiority margin was set at 5%. In the study conducted only in Canada, although all participants had seroconverted by month 7, at months 24 and 36 following first dose, fewer participants in the 2-dose than the 3-dose group remained seropositive for HPV 18 (lower 95% CI including the non-inferiority margin).

SAGE also reviewed the results from RCTs with non-randomized comparisons between girls and women. (It is important to note that young women are the age group for whom efficacy data are available.) All three trials included in the high-income strata contained results from studies conducted in Canada. In the study reported by Dobson et al. and Krajden et al, immunogenicity data from 259 girls 9 to 13 years of age, randomized to receive 2 (0,6 months) doses of HPV4

vaccine, were compared to 310 young women 16 to 26 years of age who received 3 vaccine doses (0, 2, 6 months). In HPV-048 study, immunogenicity of HPV2 vaccine was assessed following the immunization of 78 girls 9 to 14 years of age following a 2-dose schedule (0, 6 months) and 157 females 15-25 years of age following a 3-dose schedule (0, 1, 6 months). In addition, the high income strata also include data from the HPV-070[37][38] study, which was a phase IIIb RCT conducted in Canada, Germany, Italy, Taiwan and Thailand, in which HPV2 vaccine outcomes were evaluated in 476 girls 9 to 14 years of age receiving a 2-dose schedule (0, 6 months) and the same number of females 15 to 25 years of age receiving a 3-dose schedule (0, 1, 6 months).

Analysis of data from these trials showed that non-inferiority criteria for HPV16 and HPV18, based on GMC values, were met up to 36 months after vaccination. HPV-070 also reported superior GMC values in girls receiving the 2-dose schedule compared to young women receiving the licensed 3-dose schedule. Immunogenicity data on seroconversion and seropositivity were available for all three studies, and in all of them, non-inferiority criteria were fulfilled. In the study conducted only in Canada, seropositivity in girls at 24 and 36 months was higher than in young women who received 3 doses, although confidence intervals for the differences include the null effect.

SAGE also assessed additional immunogenicity data from: a trial in Europe in which 804 young women[39] 15 to 25 years of age were randomized to receive 3 doses of HPV2 vaccine using a standard (0,1,6 month) or extended (0,1,12 month) schedule; an observational study of 9-14 year old girls in Uganda[40] invited to receive a 3-dose schedule (0, 1, 6 month); and a within person comparison[41]-[44] of 9-10 year old girls in Canada after the receipt of a 2- (0, 6 month) and 3-dose (0, 6, 42 month) schedule with HPV4 vaccine. Although results from these trials supported non-inferiority of a two dose schedule, in the European trial, GMC values assessed one month following a second dose in the group receiving an extended schedule were inferior to those one month following the receipt of a standard 3-dose schedule (weighted mean difference HPV16, -1.17, 95% CI -1.30, -1.05; HPV18, -0.53, 95% CI -0.66, -0.39).

Only one RCT reviewed by SAGE (HPV-048) compared different intervals between doses. In this study, one month after the last vaccine dose in girls 9 to 14 years of age and in young women 15 to 19 and 20 to 24 years of age receiving 2 doses at 0, 6 months and at 0, 2 months, higher GMC values were noted with longer intervals between the two doses in all age groups.

SAGE also reviewed data reported through nine observational studies[40][45]-[53] and overall found their results to support the findings reported through clinical trials. However, several considerations regarding these studies were noted:

- In one Australian study[46], vaccine effectiveness for histological outcomes was estimated to be lower in girls receiving 2 doses than girls receiving 3 doses with the stronger trend observed with increasing age. However, authors did report issues associated with residual confounding, particularly those related to age at vaccination and first screening, which in Australia takes place at 18 years of age. This study included a small numbers of girls 12-13 years of age receiving fewer doses, usually at a less than a 4-6 months interval; concern was expressed that girls with incomplete immunization schedules may be different from those immunized with a 3-dose schedule.
- An observational study from Sweden[50][51] using condyloma acuminata as the outcome of interest reported greater effect of greater number of doses. However, consideration of the “buffer period” between vaccination and condyloma incidence (that was used as a proxy measure for prevalent HPV infections) and interval between doses was not

included in the interpretation of the results, and may have resulted in an artifactual difference between the 2- and 3- dose schedules. Using a longer buffer period (>5 months) to account for prevalent infections resulted in no significant effectiveness differences between 2 and 3 doses.

Immunogenicity data from trials comparing 2- and 3-dose schedules with HPV2 and HPV4 were assessed by the EMA.

For HPV2 vaccine, all data reviewed by the EMA were provided to SAGE, including detailed results from the pivotal study HPV-070 and three supportive studies HPV-048, HPV-008 and HPV-009. Data from these studies were complemented by 4-year vaccine effectiveness results obtained from the surveillance of HPV-specific infection after introduction of the National HPV Immunisation Program in the UK in girls 12-13 years of age.

In the HPV2 vaccine Assessment Report, the EMA concluded that the primary objective of non-inferiority of a 2-dose schedule based on the results from HPV-070 was met at month 7, one month after the second dose. Analysis of Geometric Mean Titre (GMT) values for anti-HPV-16 and anti-HPV-18 antibodies, when measured in 150-164, 165-194 and 195-210 day interval groups following the first dose, were similar between girls 9 to 14 years of age receiving the 2-dose (0,6 month) and females 15 to 25 receiving the 3-dose (0,1,6 month) schedule (overlapping 95% CIs); the latter group is the age group in which efficacy has been demonstrated one month after the last dose (upper limit of 95% CI for geometric mean ratio [GMR] [2-dose/3-dose]<2).

For HPV2, data from the HPV-071 study submitted by the manufacturer compared the 2-dose schedule (0, 6 months) of HPV2 vaccine vs the 2-dose schedule (0, 6 months) and 3-dose schedule (0, 2, 6 months) of HPV4 vaccine among girls ages 9 to 14 years in France, Sweden, Hong Kong and Singapore. Parallel groups of 358 subjects each were stratified by age (9-11 years and 12-14 years). Analysis of the data from this trial showed that the anti HPV-16/18 seroconversion rate of 2-dose HPV2 was non-inferior to 2- or 3-dose HPV4 one month after the last dose in initially seronegative subjects. HPV-071 also reported superior GMT values in girls receiving the 2-dose schedule of HPV2 vaccine, compared to girls receiving the 2- or 3-dose schedules of HPV4 vaccine.[54]

For HPV4 vaccine, the EMA reviewed[16] the data submitted by the manufacturer on a post-licensure, randomized, controlled, multicenter study with 3 parallel groups in 2 age strata. Girls aged 9 to 13 years were randomly assigned to receive either 2 doses (n=259) or 3 doses (n=261) and women aged 16 to 26 years were assigned to receive 3 doses of vaccine (n=310). Results from the immune responses at month 7 (one month after last vaccine dose) among girls 9-13 years of age who received 2 doses of HPV vaccine 6 months apart, showed that antibody responses to all HPV types contained in the vaccine were non-inferior and numerically higher compared to women who received 3 doses. The duration of immune responses (GMT) were studied up to 36 months after dose 1. In this study a slightly more rapid decline of antibody titres in 2-dose recipients compared to 3-dose recipients 9 to 13 years of age was noted. However, the numerical values were consistently higher in girls receiving 2 doses, compared to women receiving 3 doses, for all genotypes at all time points.

Two additional studies not included in the SAGE review regarding immunogenicity were identified through the literature search conducted for this advisory committee statement, and are summarized in Table 4. In a case-cohort[55] trial in Belgium, randomly selected serum samples were collected from 96 healthy females 10 to 55 years of age who previously received either a

3-dose (0,1,6 months) or a 2-dose schedule (0, 6 months). Antigen-antibody binding avidities were assessed with no differences observed at months 7, 24 and 48 following the first dose (Month 0) between the groups of 2-dose and 3-dose recipients. Safaeian et al. reported the results from a nested case control trial[56] conducted in Costa Rica, comparing the immunogenicity of 1-dose (n=78), 2 doses separated by one month (n=140), 2 doses separated by six months (n=52), and 3-dose schedules (n=120). At 48 months, 100% of women who received 2 doses (0, 6 months) had HPV16 and HPV18 antibody levels within the range observed among women who received all 3 vaccine doses. Similarly, among the recipients who received 2 doses (0, 1 month), 88% and 97%, respectively had HPV16 and HPV18 antibody levels within the range observed among women who received all 3-doses. Finally, among the group receiving 1-dose, 54% and 81% had HPV16 and HPV18 antibody levels at 48 months within the range observed among women who received 3 doses.

Males

Although all studies reviewed by SAGE and the EMA included only girls, there is no evidence to suggest that the results would be any different in males. Data on serum antibody responses from previously published studies designed to predict efficacy of HPV4 vaccine in individuals less than 15 years of age demonstrated much higher GMT-values (2-fold greater) in the 9 to 15 year age group, regardless of sex, than in women 16 to 23 years of age, following the receipt of 3 doses of HPV4 vaccine.

No studies published to date have looked specifically at 2 vs 3 doses of HPV vaccine in males. However, a combined analysis of immunogenicity data reviewed by NACI demonstrated non-inferiority of immune response (immunobridging) of younger males (9-15 years of age) when compared to older males (16 to 26 years of age) in whom efficacy has been demonstrated. Detailed information is available in the NACI *Update on Human Papillomavirus (HPV) Vaccines* (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/12vol38/acs-dcc-1/index-eng.php).

Table 3 summarizes antibody titres in different populations from HPV4 vaccine clinical trials (protocols 016, 018, 013, and 015).[57] These data indicate that the immune response between sexes in the 9-15 age group is comparable and that sex does not need to be considered when determining age-based recommendations for 2-dose schedules.

Table 3: Antibody titres following 3 doses of HPV4 by age and gender

Assay (competitive Luminex immunoassay [cLIA])	Girls (9 – 15 years)		Boys (9 – 15 years)		Women (16 – 23 years)	
	n	GMT* (mMU/ml)	n	GMT* (mMU/ml)	n	GMT* (mMU/ml)
Anti-HPV6	915	928.7	428	1042	2631	542.6
Anti-HPV11	915	1303.0	428	1318	2655	761.5
Anti-HPV16	913	4909.2	427	5638	2570	2293.9
Anti-HPV18	920	1039.8	429	1212	2796	461.6

*Geometric Mean Titres (mMerckUnits/ml)

V. OTHER CONSIDERATIONS

Cervical cancer screening in women who have received HPV vaccine

While HPV vaccines have been shown to be highly effective against cancer precursors caused by HPV type 16 and HPV type 18, these two HPV types are responsible for approximately 70% of cervical cancer. Those vaccinated will still be susceptible to infection from other high-risk HPV genotypes and women who were sexually active prior to receiving HPV vaccine may already have been infected with HPV type 16 or HPV type 18. All women should continue to take part in the currently recommended cervical cancer screening programs. As more females receive the vaccine, it may be possible to modify screening programs in either type or frequency of screening, or both. This area requires continued research and surveillance before guidelines are changed.

Interchangeability of vaccines

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, either vaccine may be used to complete the series. Both vaccines provide protection against HPV types 16/18 and therefore patients are likely to achieve protective antibody levels against these HPV types.

Vaccine Administration

In general, syncope can occur after any vaccination, most commonly among adolescents and young adults. To avoid serious injury related to a syncopal episode, HPV vaccine recipients should be observed for 15 minutes after vaccine administration.

Vaccine Safety and Coverage

A 2 versus 3 dose HPV vaccine series would have an impact on the number of HPV vaccine related adverse events following immunization (AEFIs) that are reported. While the accumulating evidence on the safety of the available HPV vaccines is very reassuring, as

reported multiple times by the Global Advisory Committee on Vaccine Safety (WHO),[58] reducing the number of doses in the series would reduce the opportunity for AEFIs. Similarly, reducing the number of doses in the series may have a favourable impact on vaccine coverage.

VI. RECOMMENDATIONS

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. Available data on immunogenicity indicate that 2 doses of HPV vaccine in girls 9-14 years of age are non-inferior to 3 doses when compared to 3 doses in girls 9-14 years of age or 3 doses in older females aged 15-24 years of age. While all studies reviewed included only females, there is no reason to believe that the data would be different in males. No data are currently available on fewer than 3 doses of HPV vaccine among HIV infected and other immune-compromised individuals.

In general, a schedule with fewer doses and similar effectiveness is more likely to be accepted by the public and vaccinators.[59][60] Administration of 2 doses of HPV vaccine rather than 3 may increase acceptability by students, parents, and health care professionals alike, and may lead to improved HPV immunization coverage. Administration of fewer doses of the vaccine may result in decreased operational costs. Moreover, reducing the schedule by one dose of vaccine could further minimize AEFI, compared to a 3-dose schedule.

The duration of protection of either 2 doses or 3 doses of HPV vaccine is not yet known, and scientific vigilance is encouraged to determine the need for a booster dose of the vaccine for either schedule in the future.

Based on the evidence available to date, a 2-dose HPV immunization schedule among immunocompetent 9-14 year olds may be considered by individuals and jurisdictions to allow for potential cost savings and other individual and programmatic advantages. Provinces and Territories must consider economic, legal, ethical, and political factors, as well as other local programmatic and operational factors when considering inclusion of the following recommendations in publicly funded immunization programs.

Please refer to the *2012 NACI Update Statement on HPV Vaccines* (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/12vol38/acs-dcc-1/index-eng.php#a5) for a complete list of recommendations. All of these recommendations, summarized in Table 1 above, are still applicable, except for Recommendation #10 regarding a 2-dose immunization schedule. The recommendations below replace Recommendation #10, based on evidence that has become available since the 2012 Advisory committee's statement. The new and complete set of current recommendations for HPV vaccines will be published in the updated HPV chapter in the *Canadian Immunization Guide* in the near future (http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-hpv-vph-eng.php).

Recommendation #1:
Healthy females (9-14 years of age) – NACI Grade A Recommendation

Either a 2-dose or 3-dose schedule of the HPV vaccine (Gardasil® or Cervarix®) is recommended for immunocompetent, non-HIV infected females 9-14 years of age. For a 2-dose schedule, at least 6 months between the first and second dose is recommended. If the interval between doses is shorter than 5 months, a third dose should be given at least 6 months after the first dose.

Recommendation #2:
Healthy females (≥15 years of age) – NACI Grade A Recommendation

A 3-dose schedule of the HPV vaccine (0, 2 and 6 months for Gardasil® and 0, 1, and 6 months for Cervarix®) is recommended for females 15 years of age and older, unless the first dose of HPV vaccine was administered before the age of 15 years. If the first dose was administered between 9-14 years of age, a 2-dose schedule is sufficient for females ≥15 years of age, with the second dose administered at least 6 months after the first dose.

Recommendation #3:
Healthy males (9-14 years of age) – NACI Grade B Recommendation

Either a 2-dose or 3-dose schedule of the HPV4 vaccine (Gardasil®) is recommended for immunocompetent, non-HIV infected males 9-14 years of age. For a 2-dose schedule, at least 6 months between the first and second dose is recommended. If the interval between doses is shorter than 5 months, a third dose should be given at least 6 months after the first dose.

Recommendation #4:
Healthy males (≥15 years of age) – NACI Grade B Recommendation

A 3-dose schedule of the HPV4 vaccine (Gardasil®; 0, 2 and 6 months) is recommended for males 15 years of age and older, unless the first dose of HPV vaccine was administered before the age of 15 years. If the first dose was administered between 9-14 years of age, a 2-dose schedule is likely to be sufficient for males ≥15 years of age, with the second dose administered at least 6 months after the first dose.

Recommendation #5:
Immunocompromised individuals[3] and immunocompetent HIV-infected individuals – NACI Grade I Recommendation

A 3-dose schedule of the HPV vaccine (Gardasil® for males and females - 0, 2, 6 months; or Cervarix® for females – 0, 1, 6 months) is recommended for individuals who are immunocompromised and immunocompetent HIV-infected individuals. There is insufficient evidence to recommend a 2-dose schedule in these populations; therefore a 3-dose schedule continues to be recommended for individuals who are immunocompromised and for immunocompetent HIV-infected individuals. Further study in these populations is required.

[3] For details on populations considered to be "immunocompromised", please refer to the chapter "Immunization in Immunocompromised Persons" in the *Canadian Immunization Guide* (http://www.phac-aspc.gc.ca/publicat/cig-gci/p03-07-eng.php).

VII. RESEARCH PRIORITIES

Research priorities and outstanding research questions have previously been identified through the 2005 HPV Research Priorities Workshop, as well in the 2012 NACI Statement. 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).

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

1. What is the duration of protection of a 2-dose versus 3-dose HPV immunization schedule? Will a booster dose of HPV vaccine be required for either a 2-dose or a 3-dose HPV immunization schedule?
2. What is the optimal HPV immunization schedule in HIV infected and immunocompromised populations?
3. What is the effect of a 2-dose HPV vaccine schedule compared with a 3-dose schedule on immunological and clinical outcomes in males?
4. How does the implementation of a 2-dose HPV immunization schedule affect immunization coverage?
5. How does the implementation of a 2-dose HPV immunization schedule affect rates of AEFI?
6. How can immunization coverage of HPV vaccine in recommended groups be improved?

VIII. SURVEILLANCE ISSUES

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

Epidemiology

- 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 other sub-populations, including aboriginal and immigrant populations)

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 4. Summary of evidence related to 2-dose vs. 3-dose HPV vaccine schedules (not included in SAGE report)

Evidence for effectiveness						
STUDY DETAILS					**SUMMARY**	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Gross MS, Andres R, Soren K. Human papilloma-virus (HPV) vaccination and Pap smear results in adolescent girls - Have we seen a difference? *J. Pediatr. Adolesc. Gynecol.* 2010;23(2):e 70–e71.	HPV vaccine – did not differentiate between HPV2 and HPV4	Cross sectional New York	N = 217 -Ages 11.5-20.9 -review of PAP cytology results and HPV vaccine history of all girls who received Pap tests at an adolescent clinic associated with an urban academic medical center between 01/06 and 09/09	Summary of Results: -Outcome measures -the odds ratio (OR) of having ab-normal Pap tests for girls with at least one HPV vaccine relative to girls with no HPV vaccines, adjusted by age. -The OR of having at least one abnormal Pap test for the vaccinated group was 0.254 (CI5 0.093- 0.698; P=0.008). -No comparison between one, two or three dose; however, the implication is that those with even one dose of vaccine were less likely to get abnormal Pap test results	II-3	Fair

Evidence for immunogenicity						
STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Boxus M, Lockman L, Fochesato M, Lorin C, Thomas F, Giannini SL. Antibody avidity measure-ments in recipients of Cervarix® vaccine following a two-dose schedule or a three-dose schedule *Vaccine* 32 (2014) 3232–3236.	HPV2-vaccine	Case-cohort Random serum samples selected from vaccinated cohort of previous clinical trials Belgium	N=96 -ages 10-55 -healthy female subjects who had received either 3-dose injections (Months 0,1,6) or 2-dose injections (Months 0 and 6	Summary of Results: -post-hoc Outcome measures - antigen-antibody binding avidities which reflects the degree of affinity maturation in the B-cells -measured by avidity index [AI] – the ratio of antibody concentrations in serum samples treated or not with the chaotropic agent NaSCN -analysis assumed no effect due to differences in studies and assumed avidities not affected by age Outcomes: No differences in AIs were observed at Months 7, 24 and 48 between the groups of 2-dose and 3-dose recipients	II-3	Fair -post-hoc -funded by pharma-ceutical company -clinical relevance of avidity measurement with respect to HPV is unknown

Safaeian M, Porras C, Pan Y, et al. Durable antibody responses following one dose of the bivalent human papilloma-virus L1 virus-like particle vaccine in the Costa Rica Vaccine Trial. *Cancer Prev. Res. (Phila).* 2013;6(11):1242–1250.	HPV2 vaccine	Nested Case Control -Sera analyzed was from the Costa Rica HPV16/18 Vaccine Trial Costa Rica	-one dose (n=78), 2 doses separated by one month (n=140), 2 doses separated by six months (n=52), and 3 scheduled doses (n=120, randomly selected) and seropositive women pre-trial n=113 -women in the 2-dose groups were more likely to report a higher number of lifetime partners	Outcome measures -HPV16 and -18 IgG serostatus using an L1 VLP-based ELISA that measures polyclonal antibodies -measured by geometric mean titres (GMT) -at 48 months, 100% of women who received 2 doses (0,6 months), 88% and 97%, who received 2 doses (0,1 months) and 54% and 81% who received 1 dose had HPV16 and HPV18 antibody levels within the range observed among women who received all 3 vaccine doses.	II-3	Fair -all women from original trail were randomized to receive three doses; reasons for missing vaccines were involuntary – confounding and effect modification not controlled for -adjuvant in bivalent but not in quadrivalent -adjuvant may contribute to durable B-cell response; one-dose may be sufficient?

Table 5. Levels of Evidence Based on Research Design

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 6. Quality (internal validity) Rating of Evidence

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 7. NACI Recommendation for Immunization -- Grades

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

LIST OF ABBREVIATIONS

Abbreviation	***Term***
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
CI	Confidence intervals
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
HPVWG	Human Papillomavirus Working Group
JCVI	Joint Committee on Vaccination and Immunisation
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
WHO	World Health Organization

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REFERENCES

(1) GlaxoSmithKline Inc. Product Monograph CERVARIX®, Human Papillomavirus Vaccine Types 16 and 18 (Recombinant, AS04 adjuvanted). 2014.

(2) National Advisory Committee on Immunization (NACI). Update on Human Papillomavirus (HPV) Vaccines. An Advisory Committee Statement (ACS). Canada Communicable Disease Report. January 2012;Volume 38, ACS-1:1-62.

(3) Romanowski B, Schwarz TF, Ferguson LM, et al. Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose schedule compared with the licensed 3-dose schedule: results from a randomized study. Hum Vaccin. 2011;7(12):1374-86.

(4) Block SL, Nolan T, Sattler C, et al. Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in male and female adolescents and young adult women. Pediatrics, 2006;118(5):2135-45.

(5) Einstein MH, Baron M, Levin MJ, et al. Comparison of the immunogenicity and safety of Cervarix® and Gardasil® human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18-45 years. Hum Vaccin. 2009;5(10):705-19.

(6) Dobson SR, McNeil S, Dionne M, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: A randomized clinical trial. JAMA. 2013;309(17):1793-1802.

(7) Pederson C, Petaja T, Strauss G, et al. Immunization in early adolescent females with human papillomavirus types 16 and 18 L1 virus-like particle vaccine containing AS04 adjuvant. Journal of Adolescent Health. 2007;40:564-571.

(8) National Advisory Committee on Immunization (NACI). Statement on Human Papillomavirus vaccine. An Advisory Committee Statement (ACS). Canada Communicable Disease Report. 2007;Volume 33, ACS-2:1.

(9) Canadian Immunization Committee. Recommendations on a human papillomavirus programs. Public Health Agency of Canada. December 2007:40-8:1-45.

(10) Canadian Immunization Committee. Summary of Canadian Immunization Committee (CIC) recommendations for HPV immunization programs. Canada Communicable Disease Report. April 17, 2014;40:1-19.

(11) Advisory Report of the *Comité sur l'immunisation du Québec*. HPV immunization of Québec pre-adolescents: Two or three doses? *Direction des risques biologiques et de la santé au travail*. May 2013.

(12) *Ministère la Santé et des Services sociaux. VPH : Vaccin contre les virus du papillome humain*. May 2013; Available at: http://publications.msss.gouv.qc.ca/acrobat/f/documentation/piq/chap10-4-4.pdf.

(13) BC Centre for Disease Control. Human Papillomavirus (HPV) Vaccine Extended Schedule. Health Care Professional Questions and Answers. July 2013; Available at: http://www.bccdc.ca/NR/rdonlyres/A17B3DC6-5249-4ADB-8698-104A537FAC0F/0/HPVprofessionalQA_final__Aug1_ec.pdf.

(14) *Commission fédérale pour les vaccinations (CFV). Office fédéral la santé publique. Vaccination contre les VPH (OFSP) : passage du schéma à trois doses au schéma à deux doses chez les adolescentes âgées de moins de 15 ans. Maladies transmissibles. Bulletin* 6:106-110; 2012.

(15) *Office fédéral de la santé publique (OFSP) et Commission fédérale pour les vaccinations. Plan de vaccination Suisse 2012 - Directives et recommandations*. January 2012;1.

(16) European Medicines Agency. Science Medicines Health. Committee for Medicinal Products for Human Use. Assessment Report. 1-17. February 20, 2014; Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000703/WC500167949.pdf.

(17) World Health Organization. Meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization, April 2014 - Conclusions and Recommendations. Weekly Epidemiological Record. Geneva, Switzerland. May 23, 2014;21(89:221-236).

(18) United Kingdom Government. Joint Commitee on Vaccination and Immunisation. March 2014; Available at: https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation.

(19) United Kingdom Government. Joint Committee on Vaccination and Immunisation. June 4, 2014; Available at: https://app.box.com/s/iddfb4ppwkmtjusir2tc/1/2199012147/19052160649/1

(20) European Medicines Agency. Science Medicines Health. Committee for Medicinal Products for Human Use. Assessment report. Cervarix®. International non-proprietary name: HUMAN PAPILLOMAVIRUS VACCINE (TYPES 16, 18) (RECOMBINANT, ADJUVANTED, ADSORBED). November 21, 2013; Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000721/WC500160885.pdf

(21) World Health Organization. Supplement to WHO Vaccine Position Papers. Available at: http://www.who.int/immunization/position_papers/position_paper_process.pdf?ua=1

(22) World Health Organization. Evidence based recommendations on Human Papilloma Virus (HPV) Vaccines Schedules. Background paper for SAGE discussions. March 11, 2014; Available at: http://www.who.int/immunization/sage/meetings/2014/april/1_HPV_Evidence_based_recommendationsWHO_with_Appendices2_3.pdf.

(23) World Health Organization. Guidance for the development of evidence-based vaccine-related recommendations. Strategic Advisory Group of Experts (SAGE). March 8, 2012; Available at: http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf?ua=1.

(24) World Health Organization. Terms of reference. Strategic Advisory Group of Experts (SAGE). August 2013; Available at: http://www.who.int/immunization/sage/Full_SAGE_TORs.pdf?ua=1

(25) Kreimer AR. Overview of the Costa Rica HPV vaccine trial, in Eurogin 2013 International Multidisciplinary Congress. 2013: Florence, Italy.

(26) Kreimer AR, Gonzalez P, Katki HA, et al. Efficacy of a bivalent HPV 16/18 vaccine against anal HPV 16/18 infection among young women: a nested analysis within the Costa Rica Vaccine Trial. Lancet Oncol. 2011;12(9):862-70.

(27) Kreimer AR, Rodriguez AC, Hildesheim A, et al. Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine. J Natl Cancer Inst. 2011;103(19):1444-51.

(28) Safaeien M. Immunogenicity and efficacy of hpv vaccines based on fewer doses, in Eurogin, 2013 International Multidisciplinary Congress. 2013: Florence, Italy.

(29) Arguedas A, Soley C, Loaiza C, et al. Safety and immunogenicity of one dose of MenACWY-CRM, an investigational quadrivalent meningococcal glycoconjugate vaccine, when administered to adolescents concomitantly or sequentially with Tdap and HPV vaccines. Vaccine. 2010;28(18):3171-9.

(30) Sankaranarayanan R. Trial of Two Versus Three Doses of Human Papillomavirus (HPV), Vaccine in India. [cited 2013 Nov. 15]; 2013; Available at: http://clinicaltrials.gov/show/NCT00923702.

(31) Sankaranarayanan R. 2 vs 3 doses hpv vaccine schedule: low- and middle-income countries, in Eurogin 2013 International Multidisciplinary Congress. 2013: Florence, Italy.

(32) Sankaranarayanan R, Evaluation of Fewer Than Three Doses of HPV Vaccination in India, in World Health Organization Consultation Meeting. 2013: WHO, Geneva.

(33) Krajden M, Cook D, Yu A, et al. Human papillomavirus 16 (HPV 16) and HPV 18 antibody responses measured by pseudovirus neutralization and competitive Luminex assays in a two-versus three-dose HPV vaccine trial. Clin Vaccine Immunol. 2011;18(3):418-23.

(34) *Institut national de santé publique*. HPV Vaccination in Québec: Knowledge Update and Expert Panel Proposals. Advisory Report of the *Comité sur l'immunisation du Québec* and the HPV Ad Hoc Scientific Committee. July 2012:37-59.

(35) Romanowski B, et al. Immune response to the HPV-16/18 as04-adjuvanted vaccine administered as a 2-dose or 3-dose schedule up to 4 years after vaccination, in Eurogin 2013 International Multidisciplinary Congress. 2013: Florence, Italy.

(36) GlaxoSmithKline Inc. Evaluation of the safety and immunogenicity of GlaxoSmithKline Biologicals' HPV vaccine 580299 when administered in healthy females aged 9 – 25 years using an alternative schedule and an alternative dosing as compared to the standard schedule and dosing. 2013 [cited 2013 November 14]; Available at: http://download.gskclinicalstudyregister

(37) Puthanakit T et al. Immune responses to a 2-dose schedule of the hpv-16/18 as04-adjuvanted vaccine in girls (9-14) versus 3 doses in women (15-25): A randomised trial, in Eurogin 2013 International Multidisciplinary Congress. Florence, Italy. 2013.

(38) GlaxoSmithKline Inc. Immunogenicity and safety study of GlaxoSmithKline (GSK) Biologicals' human papillomavirus (HPV)-16/18 L1 AS04 vaccine when administered according to alternative 2-dose schedules in 9 - 14 year old females. 2013 [cited 2013 Nov 14]; Available at: http://download.gsk-clinicalstudyregister.com/files/1ae03c85-a5fe-4339-a1e1-03a3d97f6793

(39) Esposito S, Birlutiu V, Jarcuska P, Perino A, Man SC, Vladareanu R, Meric D, Dobbelaere K, Thomas F, Descamps D. Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted vaccine administered according to an alternative dosing schedule compared with the standard dosing schedule in healthy women aged 15 to 25 years: Results from a randomized study. Pediatr Infect Dis J 2011 Mar;30(3):e49-55. 2011.

(40) Safaeien M. Immunogenicity of the bivalent HPV vaccine among partially vaccinated young girls in Uganda, in 28th International Papillomavirus Conference & Clinical and Public Health Workshops, Abstract book page no. 326.2012: San Juan, Puerto Rico. p. 326

(41) Sauvageau C et al. Two doses of quadrivalent hpv vaccine might be sufficient when vaccinating preadolescents, in Eurogin 2013 International Multidisciplinary Congress. 2013:Florence, Italy.

(42) Gilca V, and Sauvageau C. Immunogenicity of one and two doses of Gardasil in 9-10 year-old girls and the effect of a booster dose of Gardasil or Cervarix® given 3 years later, in World Health Organization Consultation Meeting. 2013: WHO, Geneva.

(43) Gilca V. Interchangeable use of Gardasil and Cervarix: Preliminary safety data, in 28th International papillomavirus conference. 2012: San Juan, Puerto Rico.

(44) *Institut national de santé publique. La vaccination des pré-adolescents contre les virus du papillome humain (VPH) au Québec : deux ou trois doses?* 2013 [cited 2013 Nov 14]; Available at: http://www.inspq.qc.ca/pdf/publications/1683_VaccinPreAdoVPHQc_2ou3Doses.pdf

(45) Squarzon L, et al. Evaluation of neutralizing and cross-neutralizing antibodies induced by HPV prophylactic vaccines: an independent study. Eurogin 2013.

(46) Gertig DM, Brotherton JM, Budd AC, et al. Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study. BMC Med. 2013;11:227,7015-11-227.

(47) Crowe E, Pandeya N, Brotherton JM, et al. Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities: case-control study nested within a population based screening programme in Australia. BMJ. 2014;348:g1458.

(48) Garland SM, et al. Measures of vaccine effectiveness. Abstract no. SS 22-7 in Eurogin 2013 International Multidisciplinary Congress. 2013: Florence, Italy.

(49) Leval A, Herweijer E, Ploner A, et al. Quadrivalent human papillomavirus vaccine effectiveness: a Swedish national cohort study. J Natl Cancer Inst. 2013;105(7):469-74.

(50) Herweijer E, Leval A, Ploner A, et al. Association of varying number of doses of quadrivalent human papillomavirus vaccine with incidence of condyloma. JAMA. 2014;311(6):597-603.

(51) Herweijer E, et al. Dose effectiveness of quadrivalent human papillomavirus vaccine: A national cohort study. Abstract no.OC 6-6 in Eurogin 2013 International Multidisciplinary Congress. 2013: Florence, Italy.

(52) Blomberg M, Dehlendorff C, Munk C, et al. Strongly decreased risk of genital warts after vaccination against human papillomavirus: Nationwide follow-up of vaccinated and unvaccinated girls in Denmark. Clin Infect Dis. 2013;57(7):929-34.

(53) Pollock K, et al. Early effect of the HPV bivalent vaccine on high-risk HPV prevalence and high-grade cervical abnormalities in Scotland. Abstract no. OC 6-2 in Eurogin 2013 International multidisciplinary Congress. 2013: Florence, Italy.

(54) GlaxoSmithKline. Immunogenicity and safety of 2 doses of HPV-16/18 AS04-adjuvanted vaccine compared to 2 or 3 doses of HPV-6/11/16/18 vaccine: A randomized trial. Abstract no. PH.PD04.02. International papillomavirus conference. Seatle, USA . August 2014.

(55) Boxus M, Lockman L, Fochesato M, Lorin C, Thomas F, Giannini SL, Antibody avidity measurements in recipients of Cervarix® vaccine following a 2-dose schedule or a 3-dose schedule. Vaccine 32. 2014:3232-3236.

(56) Safaeian M, Porras C, Pan Y, et al. Durable antibody responses following one dose of the bivalent human papillomavirus L1 virus-like particle vaccine in the Costa Rica Vaccine Trial. Cancer Prev Res (Phila). 2013;6(11):1242-50.

(57) Merck Canada Inc. Gardasil^{MD} Product Monograph. Kirkland, QC, 2007.

(58) World Health Organization. Global Advisory Committee on Vaccine Safety (GACVS). Safety update on HPV Vaccines. Geneva. June 13, 2013; Available at: http://www.who.int/vaccine_safety/committee/topics/hpv/130619HPV_VaccineGACVSstatement.pdf

(59) Becker-Dreps S, Otieno WA, Brewer NT, et al. HPV vaccine acceptability among Kenyan women. Vaccine. 2010;28(31):4864-7.

(60) Bramley JC, Wallace LA, Ahmed S, et al. Universal hepatitis B vaccination of UK adolescents: a feasibility and acceptability study. Commun Dis Public Health. 2002;5(4):318-20.