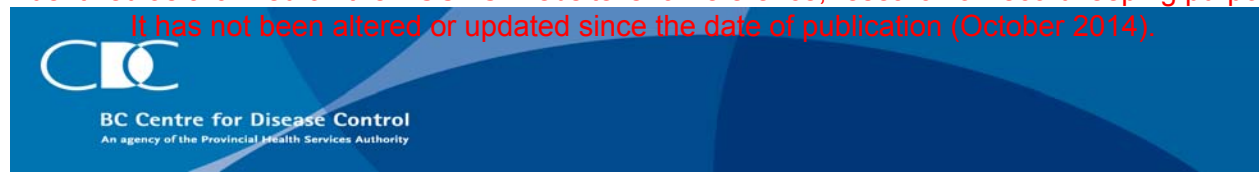




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Human Papillomavirus (HPV) Vaccine 2 Dose Schedule Q&A Document – October 2014

1. [How has the school-based HPV vaccine program changed?](#)
2. [Why has the school-based HPV vaccine program changed to 2 doses?](#)
3. [Can you tell me more about the research supporting a 2 dose HPV immunization schedule?](#)
4. [Why was this decision made for the 2014/15 school year?](#)
5. [What about girls not immunized in the school setting?](#)
6. [Is it a concern that some girls will have received a 3rd dose of HPV while others have not?](#)
7. [How will this change be communicated to parents and what resources will be available to them?](#)
8. [What if a parent insists that their daughter receive a 3rd dose of HPV vaccine?](#)
9. [How will this change be communicated to other health care providers?](#)
10. [Do the school consents need to be amended?](#)
11. [Will Panorama/PARIS be updated to reflect this schedule change?](#)
12. [What are the immunization schedules for grade 9 girls who have previously received the HPV vaccine?](#)
13. [What if a girl received her first HPV vaccine prior to 15 years of age but is now 15 years of age or older? Would she need 2 or 3 doses of HPV vaccine?](#)
14. [Is there any impact on the CERVARIX® program?](#)
15. [How long is the protection with the 2 dose series versus the 3 dose series?](#)
16. [Would it be beneficial to wait to receive the vaccine in grade 9 rather than in grade 6?](#)
17. [Are other jurisdictions adopting a 2 dose HPV vaccine schedule?](#)
18. [What are the expected benefits of moving to a 2 dose HPV vaccine program?](#)



1. How has the school-based HPV vaccine program changed?

The BC Communicable Disease (CD) Policy Committee has recommended that BC adopt a 2 dose schedule for the quadrivalent HPV vaccine (Q-HPV, GARDASIL®) for younger girls. As of October 20th 2014, immunocompetent^A females 9 to 14 years of age will now receive only 2 doses of the Q-HPV vaccine. As a result, many girls in grade 9 in the 2014/15 school year who were scheduled to receive a 3rd dose under the 'extended' dose schedule will not need to receive that 3rd dose.

Beginning October 20th 2014, girls in grade 6 will continue to be offered 2 doses of HPV vaccine. Three doses will continue to be offered to girls commencing a series on or after their 15th birthday.

The following table illustrates the new schedule:

Age at time of receipt of 1 st dose	Doses Required	Schedule (months)
9 - 14	2	0, 6
≥15 years	3	0, 2, 6

^AGirls who are known to have immune system defects associated with solid organ transplant, stem cell transplant or HIV infection are not considered "immunocompetent" and should receive 3 doses of HPV vaccine given at 0, 2 and 6 months.

2. Why has the school-based HPV vaccine program changed to 2 doses?

The BC CD Policy Committee has been contemplating a 2 dose HPV vaccine schedule since the implementation of the program in September 2008. The results from several randomized, non-randomized and observational studies from several countries including a Canadian immunogenicity trial support a 2 dose quadrivalent HPV vaccine schedule. This is based on immunogenicity data as well as effectiveness data for genital warts, HPV vaccine type specific infection and prevention of cervical abnormalities.

Based on this body of evidence, a variety of immunization expert advisory committees have now recommended the use of a 2 dose schedule. This includes the World Health Organization's Strategic Advisory Group of Experts (WHO's SAGE) on Immunization, The Swiss Federal Vaccination Committee, the Swiss Federal Public Health Office, the United Kingdom's Joint Committee on Vaccination and Immunisation (JCVI), and the European Medicines Agency (EMA).¹ On the heels of these groups' recommendations, on October 1st 2014 the National Advisory Committee on

¹ European Medicines Agency recommendation:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000703/human_med_000805.jsp



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Immunization (NACI) recommended a 2 dose HPV schedule for immunocompetent girls 9 to 14 years of age.²

3. Can you tell me more about the research supporting a 2 dose HPV immunization schedule?

Randomized controlled trials have assessed immunogenicity using 2 doses compared to 3. Results from these studies have found that for those 9 to 14 years of age, antibody titres following a 2 dose series are non-inferior to those achieved after a 3 dose series in older girls and young women.

One of these studies conducted in Canada was led by Dr. Simon Dobson working from BC Children's Hospital/ UBC Vaccine Evaluation Centre. The immune response in young girls was compared to that in older girls, the latter being the 'efficacy' age group in which earlier pivotal trials demonstrated vaccine protection against persistent infection and pre-cancerous cervical abnormalities. Females 9 to 13 years of age were allocated to either a 2 dose GARDASIL[®] schedule at 0 and 6 months (n=259) or a three dose GARDASIL[®] schedule at 0, 2 and 6 months (n=261); this latter schedule was also used for 464 females aged 16-26 years.³ Results from this study found that the younger 2 dose schedule recipients had a non-inferior immune response to the older cohort who received 3 doses and in whom protection from this response had been demonstrated in the large-scale clinical trials conducted for regulatory approval of the vaccine.

Among other immunogenicity studies reviewed, the EMA and NACI also considered a study conducted by Merck, the manufacturer of GARDASIL[®] which was a post-licensure, randomized, controlled study with 3 parallel groups in 2 age categories. Girls aged 9 to 13 were randomly assigned to receive either 2 or 3 doses and young women aged 16 to 26 were assigned to receive 3 doses of vaccine. Antibody responses to all HPV types contained in the vaccine were non-inferior and numerically higher for girls who received 2 doses compared to girls who received 3 doses.⁴

Several other randomized, non-randomized and observational studies were also reviewed by the WHO's SAGE.⁵ These included studies with clinical endpoints such as prevention of HPV infection, genital warts, and cervical abnormalities, and demonstrate protection from two doses.

² National Advisory Committee on Immunization. Update on the recommended HPV vaccine immunization schedule. Draft September 26, 2014; publication anticipated late November/ early December 2014.

³ Dobson SR, McNeil S, Dionne M, Dawar M, Ogilvie G, Krajden M, Sauvageau C, Scheifele DW, Kollmann TR, Halperin SA, Langley JM, Bettinger JA, Singer J, Money D, Miller D, Naus M, Marra F, Young E. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. JAMA. 2013 May 1;309(17):1793-802. <http://www.ncbi.nlm.nih.gov/pubmed/23632723>

⁴ 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

⁵ World Health Organization – Strategic Advisory Group of Experts on Immunization recommendation: http://www.who.int/immunization/sage/meetings/2014/april/report_summary_april_2014/en/ and see especially Evidence based recommendations on Human Papilloma Virus (HPV) Vaccines Schedules. Background paper for SAGE discussions. March 11, 2014.



4. Why was this decision made for the 2014/15 school year?

Communicable Disease Policy Committee had considered a 2 dose schedule for BC girls in the past, but wished to wait for a comprehensive review of the evidence to be completed by the National Advisory Committee on Immunization. NACI was scheduled to finalize their discussions at the October 2014 meeting. Accordingly, implementation of a 2 dose HPV program for the 2014/15 school year was discussed at the BC Immunization Committee on September 22nd, the first day of public school following a teacher's strike. The committee was supportive of implementing a change to 2 doses if recommended by NACI within the current school year but asked for a decision to be made by Communicable Disease Policy Committee as soon as possible. NACI voted on the statement on October 1st and Communicable Disease Policy Committee supported implementation of a 2 dose schedule at a special teleconference scheduled on October 6th. Each health authority has two voting members on this committee, including one Medical Health Officer and one public health nursing lead. The committee agreed to implement the change effective Monday October 20th.

It is expected that overall this change will be positively perceived by parents, health care providers and the public at large as it demonstrates the ability to respond promptly to evidence based recommendations, adding to the credibility of our publicly funded immunization programs. It avoids unnecessary immunization and associated adverse events. A 2 dose schedule is also expected to meet with higher acceptance by recipients, parents, and health care providers and may ultimately lead to higher uptake of the vaccine, and better overall prevention of cervical cancer and other HPV-related disease outcomes.

5. What about girls not immunized in the school setting?

Eligible girls 9 to 14 years of age immunized outside of the school-based program should also receive a 2 dose GARDASIL[®] schedule.

6. Is it a concern that some girls will have received a 3rd dose of HPV while others have not?

No, this does not pose a concern as this is in line with NACI's updated recommendation which support either a two or three dose schedule for the HPV vaccine in girls under 15. Given that school-based immunization programs have already commenced, it is expected that some grade 9 girls may have already received their third HPV vaccine dose.

http://www.who.int/immunization/sage/meetings/2014/april/1_HPV_Evidence_based_recommendationsWHO_with_Appendices2_3.pdf?ua=1



7. How will this change be communicated to parents and what resources will be available to them?

A “Dear Parent” letter has been provided to Medical Health Officers and public health nursing leads in the province. This letter informs parents of the schedule change and provides them with the rationale and the benefits of adopting a 2 dose program. The letter can be customized as needed at the discretion of your local Medical Health Officer and used for communicating to parents of girls in grades 6 through 9, the age group affected by the 2 dose schedule for girls under 15.

Updated HPV Health Files will also be available through HealthLinkBC <http://www.healthlinkbc.ca/> and are a good resource for parents. These will likely be available later in October. Schedule information will also be updated on BCCDC and ImmunizeBC websites.

8. What if a parent insists that their daughter receive a 3rd dose of HPV vaccine?

Explain to parents why the third HPV vaccine dose is not required for those 9 to 14 years of age. Parents who insist on a third dose for their daughter may be advised how to privately purchase a third dose.

9. How will this change be communicated to other health care providers?

A letter has been issued by Provincial Health Officer Dr. Perry Kendall to physicians including family doctors and general practitioners through the Doctors of British Columbia.

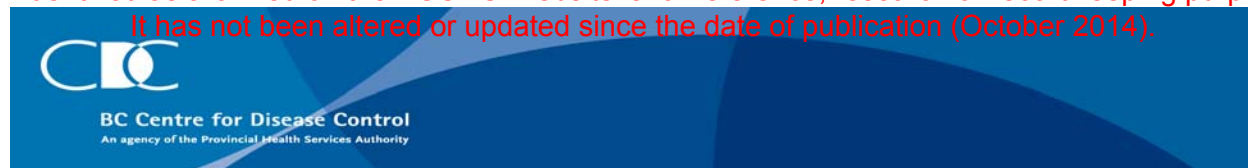
The HPV vaccine pages for GARDASIL[®] have been updated in the [Communicable Disease Manual, Chapter 2. Immunization, Section VII, Biological Products.](#)

10. Do the school consents need to be amended?

No, school consents do not need to be amended. Consent for the HPV series is still valid despite the change to the number of required doses needed for series completion. The ‘Dear Parent’ letter can be appended to consents still being distributed.

11. Will Panorama/PARIS be updated to reflect this schedule change?

Yes, the Panorama forecaster will be updated by end of October 2014 to reflect a 2 dose schedule for girls receiving a first dose prior to the 15th birthday. The minimum interval validation of the 2nd dose will be 5 30-day calendar months (150 days) but the “eligible” (earliest brought forward) interval will be 6 months calculated as 6 x 28 days and the “due” (recommended) interval will be 6 calendar months. In the forecaster, girls whose first dose was given prior to the 15th birthday but



who do not meet the minimum interval of 150 days to a 2nd dose will be forecast on a standard 3 dose schedule. The PARIS forecaster will also be updated but the anticipated date of this change is to be determined.

12. What are the immunization schedules for grade 9 girls who have previously received the HPV vaccine?

For girls who have received 1 or more doses prior to the 15th birthday:

Doses Previously Received	Dose(s) Required to Complete Series
2	None, if prior doses were given at least 5 months apart. 1 more dose if previous 2 doses were given less than 5 months apart.
1	1 dose at least 6 months after the earlier dose.
3	No further doses required if previous 3 doses were given at valid intervals. See Immunization Manual, Section II.

13. What if a girl received her first dose of HPV vaccine prior to 15 years of age but is now 15 years of age or older? Would she need 2 or 3 doses of HPV vaccine?

As long as the first dose of HPV vaccine was administered after age 9 and before the 15th birthday, a total of 2 doses is sufficient for girls who are now 15 years of age or older. The second dose of HPV vaccine should be administered at least 6 months after the first dose.

14. Is there any impact on the CERVARIX® program?

No, there is no impact to the 3 dose CERVARIX® program for women born prior to 1994. CERVARIX® is approved for use as a series of two doses for girls aged 9-14 years, while the BC CERVARIX® program is for young women beyond this age.

15. How long is the protection with the 2 doses series versus the 3 dose series?

The duration of protection of either a 2 dose or 3 dose HPV series is not yet known. Antibody declines occur in both 3 and 2 dose recipients and reach similar plateaus. Further research is needed to determine whether a booster dose of the vaccine for either schedule is required.



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16. Would it be beneficial to wait to receive the vaccine in grade 9 rather than in grade 6?

No. In randomized controlled trials involving pre-adolescents and adolescents, antibody concentrations after immunizations were found to be inversely correlated with age. Higher antibody levels were noted in younger girls compared to older girls and women, indicating that this vaccine is more immunogenic when administered at a younger age. As well, earlier immunization is important to prevent HPV infection which may occur if immunization is delayed to later in adolescence because of onset of sexual activity.

17. Are other jurisdictions adopting a 2 dose HPV vaccine schedule?

All jurisdictions in Canada are currently offering HPV immunization in publicly-funded programs to females in grades 4 through 8. All but Quebec and BC are currently offering a 3 dose HPV immunization schedule. Since 2013, Quebec has used a 2 dose vaccine schedule with an interval of at least 6 months between doses for girls in grade 4. With the anticipated publication of the updated NACI statement supporting a 2 dose HPV vaccine schedule, it is expected that most provinces/territories will move in this direction.

18. What are the expected benefits of moving to a 2 dose HPV vaccine program?

Benefits of this change include but are not limited to the following:

- A reduction in the number of reported HPV vaccine related adverse events following immunization (AEFIs). Despite the excellent safety profiles of HPV vaccines, reducing the number of doses in the series will reduce the opportunity for AEFIs.
- A reduction in the number of doses in the series may result in parents being more inclined to consent for the series. This may help to increase HPV vaccine coverage.
- It demonstrates responsiveness to emerging evidence and accordingly may help to improve public credibility in BC's immunization programs and vaccines at large.
- It highlights the excellent effectiveness profile of the HPV vaccine.
- It showcases the contribution of Canadian studies in the adoption of a two dose schedule.