



BC Centre for Disease Control  
AN AGENCY OF THE PROVINCIAL HEALTH SERVICES AUTHORITY



ImmunizeBC

## HUMAN PAPILLOMAVIRUS (HPV) VACCINE EXTENDED SCHEDULE

### HEALTH CARE PROFESSIONAL QUESTIONS AND ANSWERS

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### 1. As of September 2013, how is the school based HPV vaccine 3 dose extended schedule being changed?

Girls and young women born in or after 1994 will be on a revised HPV vaccine extended dose schedule. Girls will receive 2 doses in grade 6 and a 3<sup>rd</sup> dose in grade 9. In grade 6 the 2 doses will be offered 6 months apart, as has been done since the 2010/11 school year.

This recommendation follows a general principle of vaccinology in that intervals longer than those recommended between doses in a vaccine series do not lead to a reduction in final antibody concentrations. As a general rule, interruption of a series for any reason does not require starting the series over again, regardless of the interval elapsed.

### 2. Why is the school based HPV vaccine 3 dose extended schedule being changed?

This change is being made for operational reasons. Public health nurses offer tetanus-diphtheria-pertussis (whooping cough) vaccine to students in grade 9 in BC. Therefore, grade 9 offers a platform for co-administration of other needed vaccines. While earlier plans had been to consider giving a 3<sup>rd</sup> dose in grade 11, this would be more resource intensive. As well, based on BC Ministry of Education data, school leaving rates are higher after grade 10 with 11% of students not returning for grade 11, compared to only 3% of students leaving each year after grades 6 through 8.

### 3. Who qualifies for the school based HPV vaccine 3 dose extended schedule?

The school based HPV vaccine 3 dose extended schedule will be offered to girls who are receiving/have received their 1<sup>st</sup> and 2<sup>nd</sup> doses of HPV vaccine in grade 6. Since September 2010, grade 6 girls have been offered 2 doses of the HPV vaccine separated by 6 months. The first such cohort enters grade 9 in September 2013.

### 4. What if a girl does not receive 2 doses of HPV vaccine separated by 6 months in grade 6?

Every effort should be made to vaccinate girls on the school based HPV vaccine 3 dose extended schedule. However, as with other inactivated vaccines, a delay in giving a subsequent dose does not mean you should restart the entire series. The missed dose should be given as soon as the client presents. If a girl is no longer in grade 6 when she presents for her 2<sup>nd</sup> dose of the HPV vaccine she should complete her series on the 0, 2 and 6 months schedule, with the final dose at least 12 weeks after the delayed 2<sup>nd</sup> dose. This is to ensure series completion in an already delayed series.

## 5. What about girls not immunized in grade 6?

Girls and young women born in or after 1994 who were eligible but didn't receive the HPV vaccine in grade 6, or who did not complete the recommended number of doses, should be offered 3 dose series of the HPV vaccine on the 0, 2 and 6 month schedule.

A public health nurse at a school clinic or local health unit may immunize such girls. In addition, a family doctor or pharmacist may provide the HPV vaccine to eligible girls and should provide a record of immunization. Also such providers should be asked to report back GARDASIL® administration to the local health unit with sufficient data to update the immunization registry (Panorama or PARIS).

## 6. Can grade 6 girls receive their school based HPV immunizations on the 0, 2 and 6 month schedule?

No. Parents who are concerned about the extended 3 dose schedule should be reassured that the new schedule offers excellent protection.

## 7. How many doses of the HPV vaccine will be offered to grade 9 girls?

Girls who have received 2 doses in grade 6 separated by 6 months will be offered a 3<sup>rd</sup> dose of HPV vaccine in grade 9. All other girls who present in grade 9 are also eligible to commence and/or complete a 3 dose HPV vaccine series. For previously unimmunized girls, a 3 dose HPV vaccine series should be offered on the 0, 2 and 6 month schedule. At the discretion of the health authority, administration of the additional doses required may take place in public health units rather than the school setting.

## 8. Is informed consent provided in grade 6 for the HPV vaccine still valid in grade 9?

No, because of the long interval between the 2<sup>nd</sup> and 3<sup>rd</sup> doses, health authorities will need to re-consent girls for their 3<sup>rd</sup> HPV vaccine dose in grade 9. The BC Immunization Committee (BCIC) Informed Consent Working Group (ICWG) has revised the grade 9 consent form to support the school based HPV vaccine 3 dose extended schedule.

## 9. What about girls who receive 2 doses of the HPV vaccine in grade 6 but are lost to follow-up and don't receive a 3<sup>rd</sup> dose in grade 9?

Current research would indicate that such girls may have adequate protection from 2 doses of the HPV vaccine. Additional information will be available in future years. In the meantime, should such girls re-present at a later age, a 3<sup>rd</sup> dose should be offered.

## 10. How will HPV immunization uptake rates be reported for girls in grades 6 and 9?

HPV immunization uptake rates for girls in grades 6 and 9 will be reported through routine school-based immunization coverage assessment:

- Grade 6 girls will be considered up-to-date for the HPV vaccine if they have received 2 doses of the HPV vaccine with at least 6 months between doses, or a valid 3-dose series\* of the HPV vaccine, by June 30 of the year they complete grade 6.
- Grade 9 girls will be considered up-to-date for the HPV vaccine if they have received a valid 3-dose series\* of the HPV vaccine, by June 30 of the year they complete grade 9.

\*A valid 3-dose series of the HPV vaccine is defined as 3 doses with at least 4 weeks between 1<sup>st</sup> and 2<sup>nd</sup> dose and at least 12 weeks between the 2<sup>nd</sup> and 3<sup>rd</sup> dose.

- HPV immunization uptake rates are posted at:  
<http://www.bccdc.ca/imm-vac/BCImmunizationCov/schoolagecoverage/default.htm>

## 11. What about girls from another jurisdiction who have an incomplete HPV immunization series started with CERVARIX® or GARDASIL®?

Girls born in or after 1994 who have initiated but not completed a HPV vaccine series in another jurisdiction should complete their series in BC using GARDASIL® on a 0, 2 and 6 month schedule. Both HPV vaccines (CERVARIX® and GARDASIL®) provide protection against HPV types 16/18 and therefore clients are considered adequately immunized against both of these oncogenic strains if either vaccine is used.

## 12. What about girls from another jurisdiction who completed their HPV immunization series with CERVARIX®?

Girls born in or after 1994 who have completed a CERVARIX® vaccine series in another jurisdiction are considered up-to-date for their HPV vaccine series. Both HPV vaccines (CERVARIX® and GARDASIL®) provide protection against HPV types 16/18 and therefore clients are considered adequately immunized against both of these oncogenic strains if either vaccine is used.

## Background

## 13. What is the history of the school based HPV vaccine program for girls in BC?

The HPV vaccine program started in September 2008 in a 3-dose series, with all 3 doses given in grade 6. In September 2010, it was changed to an 'extended' dose schedule with 2 doses given 6 months apart in grade 6 and a planned 3<sup>rd</sup> dose to be given 60 months after the 1<sup>st</sup>

dose in grade 11. This change was made because emerging data indicated that protection against HPV infection as measured by antibody levels was as good after 2 doses in younger girls as after 3 doses in young women in whom evidence of protection against persistent infection and precancerous lesions had been shown in clinical trials.

School based HPV vaccine program for girls in BC:	
September 2008	Program introduced - school based 3 dose series for grade 6 and 9 girls
September 2010	Extended schedule introduced - 2 doses for girls in grade 6 and planned 3 <sup>rd</sup> dose in grade 11
June 2011	School based 3 dose series for grade 9 girls ends
September 2013	Extended schedule change - 3 <sup>rd</sup> dose of HPV vaccine to be offered in grade 9

#### 14. Is it common for a vaccine schedule to change?

Yes. When new vaccine programs are introduced it is expected that recommended schedules may change over time. As new evidence emerges regarding factors such as vaccine efficacy and duration of immunity, immunization schedules may change. Examples of immunization schedules in BC that have changed over time are: pneumococcal conjugate, varicella, hepatitis B, measles and mumps vaccines. In each of these cases, schedules were successfully changed to reflect the best evidence as it became available.

#### 15. In the future will there be any other changes to the HPV vaccine program?

Yes, this is quite possible. Immunization programs change over time when new knowledge emerges about the number of doses needed for long term protection. Changes may be made to the immunization schedule in the future for the HPV vaccine including timing, number of doses and need for booster doses. As well, newer HPV vaccines that protect against a larger number of HPV virus strains may become available in the future.

#### 16. Is a 3 dose HPV vaccine series necessary for full protection against HPV types 6, 11, 16 and 18?

The HPV vaccine used in the BC school-age program for girls (GARDASIL®) is approved by Health Canada and recommended by the National Advisory Committee on Immunization (NACI) for use in a 3 dose series. Several studies are ongoing to examine the protection from fewer than 3 doses. The 3<sup>rd</sup> dose is being offered at this time to ensure sustained protection against HPV types 6, 11, 16, 18 into sexually active years of life. As new information emerges, the scientific and immunization policy groups in BC and Canada will consider whether 2 doses are sufficient and the optimal timing of those doses.

## 17. Why are extended HPV vaccine schedules being studied?

Beginning in 2005, there was interest expressed nationally and internationally in investigating extended or alternate HPV vaccine dosing regimes. Priority was given to this research due to: the recognized high efficacy of the HPV vaccine; data indicating higher immune responses in younger recipients; the vaccine manufacturer's limited rationale regarding the recommendation of the 0, 2, and 6 month schedule; and an interest in optimizing the schedule for improved cost-effectiveness that might allow for broader use of the vaccine. The national interest resulted in the funding of the BC-led national study investigating a 2 dose alternate schedule in girls.

There are a number of other studies investigating different HPV vaccine schedules in addition to the study mentioned above. Non-governmental agencies, such as the Program for Appropriate Technology in Health (PATH), are currently evaluating additional alternate and extended schedules (0-3-9 month, 0-6-12 month, and 0-12-24 month) in ongoing trials against the standard 0, 2 and 6 month schedule. For more information about PATH and their HPV vaccine studies, go to <http://www.path.org/vaccineresources/hpv.php>. As well, the manufacturer of CERVARIX® is investigating a 2 dose pediatric vaccine schedule. Results of these studies will be available at a later time.

## 18. Are other jurisdictions in Canada using a school based extended HPV vaccine schedule?

Yes. Since 2008, Québec has used a 0, 6 and 60 month school based extended HPV vaccine schedule for girls in grade 4. The provision of the 3<sup>rd</sup> dose of the HPV vaccine to grade 9 girls was to commence this fall. However, Québec's HPV vaccine schedule has now been updated to 2 doses in grade 4 only, without a 3<sup>rd</sup> dose. Further, Québec is starting a 10 year effectiveness study with their original 4<sup>th</sup> grade cohort (who is now in grade 9). If future research indicates a 3<sup>rd</sup> HPV vaccine dose is required, Québec will follow up with girls as all their vaccination data are in a central registry.

Information on the 2 dose HPV vaccine schedule will be available on Québec's website: Santé et Services Sociaux Québec

[http://www.msss.gouv.qc.ca/sujets/santepub/vaccination/index.php?vaccin\\_contre\\_vph\\_en](http://www.msss.gouv.qc.ca/sujets/santepub/vaccination/index.php?vaccin_contre_vph_en)

## 19. Is this an off label schedule when compared to the GARDASIL® product monograph?

Yes, this is an off label schedule. The decision to use an off label schedule was approved by the BC Communicable Disease Policy Advisory Committee in 2010. The committee recommendation was based on the 24-month results of a HPV vaccine study lead by BC pediatric infectious disease specialist Dr. Simon Dobson. This study called BCGov01, had found that the immune protection in girls aged 9-13 years given 2 doses of the HPV vaccine is non-inferior to that in girls aged 16-26 years given 3 doses. Based on these results, the committee recommended using a 2 dose series in this age group with the proviso that a 3<sup>rd</sup> dose would be given at a later date. It was initially envisioned that the 3<sup>rd</sup> HPV vaccine dose

would be given 60 months after the 1<sup>st</sup>, pending the availability of results from other studies. The BCGov01 study is now complete and the results at 36 months of follow-up are provided in its abstract ([see Appendix A](#)).

20. Can you tell me more about the QUEST study that is evaluating a 2 versus 3 dose HPV vaccine schedule?

Yes. There is an ongoing national study called 'QUEST' lead by Dr. Simon Dobson currently enrolling girls and young women. The QUEST study has been designed to look at the protection from 2 or 3 doses of HPV vaccine in girls immunized on these two different schedules with continuing enrolment in the study for up to 10 years after receipt of the 1<sup>st</sup> HPV vaccine dose. The study is seeking to recruit 8,666 girls and young women from across Canada ranging from about 14 to about 18 years of age when the study started. Girls will be asked to take part in this study if they have received either 2 or 3 doses of the Quadrivalent HPV vaccine on the public health program in the 5 provinces, or who were in the 2007 – 2011 BCGov01 study. Enrolment is being conducted in Alberta, British Columbia, Nova Scotia, Prince Edward Island and Québec.

As an immunization provider you can stay informed and up-to-date by signing up for the QUEST newsletter. To sign up go to <http://questhpvstudy.ca/quest-newsletter/>



## Resources

British Columbia Centre for Disease Control. Communicable Disease Control Manual. (2013). Chapter II Immunization Program Section VII Biological Products Human Papillomavirus. Retrieved from <http://www.bccdc.ca/dis-cond/comm-manual/CDManualChap2.htm>

British Columbia Centre for Disease Control (BCCDC)  
<http://www.bccdc.ca/imm-vac/ForHealthProfessionals/default.htm>

Dobson SR, McNeil S, Dionne M, Dawar M, Ogilvie G, Krajden 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. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/23632723>

GARDASIL® Product Monograph (2011). Merck. Retrieved from [http://www.merck.ca/assets/en/pdf/products/GARDASIL-PM\\_E.pdf](http://www.merck.ca/assets/en/pdf/products/GARDASIL-PM_E.pdf)

HealthlinkBC <http://www.healthlinkbc.ca/servicesresources/healthlinkbcfiles/index.html>

ImmunizeBC <http://immunizebc.ca/healthcare-professionals>

National Advisory Committee on Immunization. (2012). Canadian Immunization Guide. Part 4 Active Vaccines Human Papillomavirus Vaccine. Retrieved from <http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-hpv-vph-eng.php>

National Advisory Committee on Immunization. (2012). Update on Human Papillomavirus (HPV) Vaccines. Canada Communicable Disease Report; 38(ACS 1). Retrieved from <http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/12vol38/acs-dcc-1/index-eng.php>



## Appendix A

The 36-month results of the HPV vaccine immunogenicity study called BCGov01 have recently been published and the abstract is below:

Immunogenicity of 2 Doses of HPV Vaccine in Younger Adolescents vs 3 Doses in Young Women A Randomized Clinical Trial
Simon R. M. Dobson, MD; Shelly McNeil, MD; Marc Dionne, MD; Meena Dawar, MD; Gina Ogilvie, MD; Mel Krajden, MD, PhD; Chantal Sauvageau, MD; David W. Scheifele, MD; Tobias R. Kollmann, MD, PhD; Scott A. Halperin, MD; Joanne M. Langley, MD; Julie A. Bettinger, PhD; Joel Singer, PhD; Deborah Money, MD; Dianne Miller, MD; Monika Naus, MD; Fawziah Marra, PharmD; Eric Young, MD
JAMA. 2013;309(17):1793-1802. doi:10.1001/jama.2013.1625.
<b>Importance</b> Global use of human papillomavirus (HPV) vaccines to prevent cervical cancer is impeded by cost. A 2-dose schedule for girls may be possible.
<b>Objective</b> To determine whether mean antibody levels to HPV-16 and HPV-18 among girls receiving 2 doses was noninferior to women receiving 3 doses.
<b>Design, Setting, and Patients</b> Randomized, phase 3, postlicensure, multicenter, age-stratified, noninferiority immunogenicity study of 830 Canadian females from August 2007 through February 2011. Follow-up blood samples were provided by 675 participants (81%).
<b>Intervention</b> Girls (9-13 years) were randomized 1:1 to receive 3 doses of quadrivalent HPV vaccine at 0, 2, and 6 months (n = 261) or 2 doses at 0 and 6 months (n = 259). Young women (16-26 years) received 3 doses at 0, 2, and 6 months (n = 310). Antibody levels were measured at 0, 7, 18, 24, and 36 months.
<b>Main Outcomes and Measures</b> Primary outcome was noninferiority (95% CI, lower bound >0.5) of geometric mean titer (GMT) ratios for HPV-16 and HPV-18 for girls (2 doses) compared with young women (3 doses) 1 month after last dose. Secondary outcomes were noninferiority of GMT ratios of girls receiving 2 vs 3 doses of vaccine; and durability of noninferiority to 36 months.
<b>Results</b> The GMT ratios were noninferior for girls (2 doses) to women (3 doses): 2.07 (95% CI, 1.62-2.65) for HPV-16 and 1.76 (95% CI, 1.41-2.19) for HPV-18. Girls (3 doses) had GMT responses 1 month after last vaccination for HPV-16 of 7736 milli-Merck units per mL (mMU/mL) (95% CI, 6651-8999) and HPV-18 of 1730 mMU/mL (95% CI, 1512-1980). The GMT ratios were noninferior for girls (2 doses) to girls (3 doses): 0.95 (95% CI, 0.73-1.23) for HPV-16 and 0.68 (95% CI, 0.54-0.85) for HPV-18. The GMT ratios for girls (2 doses) to women (3 doses) remained noninferior for all genotypes to 36 months. Antibody responses in girls were noninferior after 2 doses vs 3 doses for all 4 vaccine genotypes at month 7, but not for HPV-18 by month 24 or HPV-6 by month 36.
<b>Conclusions and Relevance</b> Among girls who received 2 doses of HPV vaccine 6 months apart, responses to HPV-16 and HPV-18 one month after the last dose were noninferior to those among young women who received 3 doses of the vaccine within 6 months. Because of the loss of noninferiority to some genotypes at 24 to 36 months in girls given 2 doses vs 3 doses, more data on the duration of protection are needed before reduced-dose schedules can be recommended.