Q1. **What is being changed in the BC HPV vaccine schedule in 2010-2011 and why?**

Girls between the ages of 9-13 years will be on an extended dosing schedule of the HPV vaccine, starting September 2010. Two doses will be offered, six months apart. A 3rd dose will be given in 60 months.

Girls who have had the first dose of the HPV vaccine series between the ages of 9-13 years on the previous schedule of 0, 2, and 6 months should be offered a second dose on presentation, providing it is at least 6 months since the first dose. Girls presenting at a longer interval than 6 months between the 1st and 2nd doses should also be offered a 2nd dose. In both of these situations, a 3rd dose will be given in 60 months. 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.

This change will put the HPV vaccine onto the same schedule in grade 6 as the hepatitis B vaccine. Two doses of HPV vaccine are protective in this age group due to their strong immune response.

Q2. **Is it common for a vaccine schedule to change so soon after a new vaccine is introduced?**

Yes. When new vaccine programs are introduced it is expected that recommended schedules may change as new evidence emerges regarding factors such as vaccine efficacy and duration of immunity. Pneumococcal conjugate, measles and mumps vaccine schedules have all changed over time. In each of these cases, schedules were successfully changed to reflect the best evidence as it became available.

Q3. **Who qualifies for the HPV vaccine extended schedule?**

The extended HPV schedule will be offered to girls who are receiving/ have received their first dose of HPV vaccine between the ages of 9-13 years.

Girls who are receiving/ who have received the first dose of HPV vaccine as part of the existing grade 9 program (final year starting in September 2010) require 3 doses, and will continue to receive HPV vaccine on a 0, 2 and 6 month schedule.

Girls who are known to have immune system defects associated with solid organ transplant, stem cell transplant, or HIV infection, (regardless of age at series commencement) should receive HPV vaccine in the three dose schedule at 0, 2, and 6 months. The immunosuppressed state results in a less robust immune response. Additionally, girls with such conditions are at risk of persistent HPV infection and associated HPV disease if they become infected.
Q4. Are other jurisdictions using an extended HPV vaccine schedule?
Yes. A 0, 6 and 60 month schedule is used in Quebec and has been since 2008 in the grade 4 program. The third dose has not yet been administered.

Interest in using extended schedules is widespread. 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.

Q5. Is this an off label schedule based on the current Gardasil product monograph?
Yes it is. However, the BC Communicable Disease Policy Advisory Committee has reviewed the results at 24 months of a study of two doses given at 0 and 6 months to girls aged 9-13 years and has recommended this schedule for BC girls in this age group. Results of the same study will be reviewed at 36 months, and should be available in late spring 2011. The third dose is being planned at this time to ensure sustained protection into sexually active years of life.

Q6. What dose volume will be used in the 9-13 year age group extended schedule?
For all HPV doses, the dose volume remains 0.5 mL.

Q7. Will HPV dose #2 timing coincide with the hepatitis B vaccine scheduling?
Yes, in the school vaccination setting, these will both be offered six months after dose one. However, if catching up girls after the first clinic, be aware that minimum intervals for hepatitis B and HPV vaccine extended dose schedule for 9-13 year olds may be different depending on the brand of hepatitis B vaccine used for the two doses. Engerix requires a minimum interval of six months; Recombivax HB four months. When using the extended schedule for girls between the ages of 9-13 years, the minimum interval between HPV dose 1 and 2 is 6 months.

Q8. What is the procedure if girls do not receive their 2nd dose on time?
Every effort should be made to vaccinate all clients on 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. When using the 9-13 years extended schedule, the minimum interval between dose 1 and 2 is 6 months.

Q9. What process will be in place to track girls for receipt of dose #3?
All HPV vaccines given in schools are recorded by nurses in 2 steps: a) manually on consent forms and b) in registries (iPHIS or PARIS). Registries allow for bringing forward clients for doses for which they are eligible. As well, all vaccine recipients should be reminded to hold on to their record of vaccination, for each dose given, should they move out of province and need to complete their series elsewhere, and as a permanent record of their immunization.

Q10. Can parents ask that their girls receive the 0, 2, and 6 month schedule?
No. Parents who are concerned about the new schedule should be reassured that the new schedule offers protection as good as that of the 0, 2, and 6 month schedule. Parents who insist on having a two month dose could be referred to private purchase of that dose through a primary health care provider, pharmacist or travel clinic.

Q11. Are school consents being changed to reflect the new schedule?
For the 2010-2011 school year, grade 6 consent forms were sent out with a cover letter, explaining the schedule change. For the 2011-2012 grade 6 school year, the informed consent working group will revise the consent form to list only the 2 doses given in grade 6.
Q12. What about follow-up of girls who move between iPHIS and PARIS health units?
This would be handled according to existing protocols for children who migrate between health units using different immunization registries in BC.

Q13. What about girls who leave the province after their first 2 doses?
If a girl leaves the province after her first dose she will have a record of vaccine receipt. She will then be followed up with as per procedure in that jurisdiction.

Q14. Will girls on the extended schedule need to be re-consented for the 3rd dose?
Yes. Because of the long interval between the second and third dose, health authorities should plan to re-consent girls before their third dose.

Q15. Will we have to check the record of every girl who is getting the 60 month dose # 3 to see how many doses they received in between the ages of 9-13 years?
When the 60 month dose is offered, the girls’ prior record in the immunization registry will be brought forward for review. As well, parents will be able to record previous HPV dose receipt on the consent form.

Q16. Will girls who missed commencing their series between the ages of 9-13 and present at older age qualify for vaccination according to the extended schedule?
No. Girls who missed commencing the series between the ages of 9-13 years and who present later for vaccine should be vaccinated on the 0, 2, and 6 month schedule.

Q17. How many doses will grade 9 girls be offered?
As in previous years, girls older than 13 years will be given 3 doses of HPV vaccine using the 0, 2 and 6 month schedule. This is the final year of the grade 9 program. Girls who missed receiving the series in grade 9, and who present later for vaccine, should be vaccinated according to the 0, 2 and 6 month schedule.

Q18. What is the evidence that girls who receive two doses at 0 and 6 months have immune protection against HPV?
A study led by Dr. Simon Dobson from BC and conducted in three Canadian provinces found that the immune protection in girls aged 9-13 years given two doses of HPV vaccine is non-inferior to that in girls aged 16-26 years given three doses. This older group is the age group in which clinical trials for efficacy were conducted.

The study compared the quadrivalent HPV vaccine given in two doses at 0 and 6 months to 3 doses given in the standard schedule of 0, 2 and 6 months. It concluded that at 7 and 24 months from the start of the series, girls aged 9-13 on the two dose schedule demonstrated significantly higher antibody titres, higher seroconversion rates, and non-inferiority compared to young adult women (16-26 years) who received 3 doses in the standard schedule. Non-inferiority was assessed using geometric mean titres (GMT) of the antibody levels against HPV types 16, 18 (oncogenic) and 6, 11 (genital warts) using the standard criteria for vaccine clinical trials. Non-inferiority criteria are met when the lower bound of the adjusted 95% confidence interval of GMT ratios is greater than 0.5.

Although this study showed that compared to 9-13 year old girls on the standard 3 dose schedule, girls who received the 2 dose schedule had a lower response to HPV type 18, their memory B cells were as numerous as those in girls receiving 3 doses. This suggests comparable maintenance of immunity to HPV type 18.
Q19. **What led to the design of this study?**

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 aged 9–13 years.

There are a number of other studies investigating different HPV vaccine schedules, and these were outlined above (see Q4). As well, the manufacturer of Cervarix, a bivalent HPV vaccine, is currently investigating a 2 dose paediatric vaccine schedule. Results of these studies will be available later.

Q20. **Can you provide a link to the evidence for the two dose HPV vaccine schedule study?**

The results of this study are provided below in the form of the abstract presented at the 27th International Papillomavirus Conference. The abstract is provided below, and can be accessed online at [http://hpv2010.org/](http://hpv2010.org/) search term: Dobson.
A TWO DOSE HPV VACCINE SCHEDULE IN GIRLS: IMMUNOGENICITY AT 24 MONTHS

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**Background:** One month after the second dose of a two dose (0,6 month) schedule using quadrivalent HPV vaccine (Q-HPV) in 9-13 year old girls, the antibody responses to HPV-16,18,6,11 were non-inferior to 3 dose regimens in both young adult women and 9-13 year old girls. Presented is follow up immunogenicity at 24 months post dose 1.

**Objectives:** To determine if the antibody responses to HPV-16,18,6,11 remain non-inferior at month 24, following a 2 dose pediatric regimen as compared to a 3-dose adult regimen.

**Methods:** In this phase III, post licensure randomized controlled multi-centre trial the three groups and treatment regimens were as follows: 1) Healthy girls, 9-13 years old–2 doses Q-HPV vaccine at 0, 6 months, (n=194) 2) Healthy girls, 9-13 years old–3 doses of Q-HPV vaccine at 0, 2 and 6 month (n=187) 3) Healthy 16-26 year olds–3 doses of Q-HPV vaccine at 0, 2 and 6 months (n=203) Blood at Month 24 was evaluated using Merck Competitive Luminex ImmunoAssay (cLIA) to assess serum antibody concentrations to HPV-16,-18,-6 and -11. An Analysis of Variance (ANOVA) to test differences in the Geometric Mean Titres (GMTs) were performed. Non-inferiority of any treatment arm was declared if lower bounds of the 95%CIs of GMT ratios were greater than 0.5.

**Conclusions:** Following a 2 dose pediatric regimen, antibody responses to HPV-16, 18, 6, 11 remained non-inferior at month 24, as compared to a 3-dose regimen in young adult women. Compared to a 3 dose pediatric regimen, a dose 2 pediatric regimen was non-inferior for HPV-16, 6, 11 but not for HPV-18.
Q21. What about girls who receive two doses of HPV vaccine this coming year in grade 6 but are lost to follow-up and don’t receive a third dose?

The results of the above study would indicate that such girls may have adequate protection for long term duration of immunity. Additional information will be available in future years.

The duration of the immune response can be inferred from the height of the GMTs achieved. Data on those immunized in efficacy trials indicates that this protection is expected to be more than 15 years. In the 2-dose HPV vaccine study, girls who received the two dose schedule had a non-inferior immune response to the efficacy cohort.

Q22. Do immunization service providers have a role in obtaining consent for evaluation of the immunization programs?

Yes. The recommended communication to all recipients of vaccines should include the following: “You may be contacted to request your participation in the evaluation of this [vaccine] program.”

The HLTH 2384 “Consent for Grade 6 immunizations” form contains a similar statement. This phrase has been evaluated by provincial government legal counsel as adequate consent to future requests for participation in clinical evaluation of vaccine programs.