# HPV Q & A #3
# September 3, 2009

# 1.0 HPV VACCINE

## 1.1 Which vaccine is being used in the BC HPV vaccine program?

The vaccine used in the BC publicly funded HPV vaccine program for girls in grades 6 and 9 since the introduction of the program in September 2008 is Gardasil™ (Merck Frosst Canada).

As of September 2009, Gardasil™ is the only HPV vaccine approved for use in Canada. This vaccine has been approved for use in 112 countries, with over 45 million doses distributed worldwide in more than 77 countries. As of July 2009, 26 national authorities had recommended its use and it has been funded through public sector programs in 25 countries.

## 1.2 Is the HPV vaccine safe?

In both clinical trials conducted for the testing of the vaccine prior to its approval, and in post-marketing surveillance, this vaccine has been shown to be safe. A sufficient number of doses have now been administered to identify the occurrence of even rare serious events.

Side effects related to injection of the vaccine include pain, redness and swelling at the injection site. These are common and resolve within a few days. Fainting within a short time following vaccination has been observed with this vaccine in BC and in other countries. Fainting is sometimes seen with vaccination, and is more common in teens and girls. It is short lasting and the only serious risk associated with fainting is related to injury from a fall. Fainting can alarm observers because it is sometimes associated with 'tonic-clonic' movements that are jerking movements of the limbs that have the appearance of a seizure, but these are not true seizures as seen with epilepsy. Public health staff have procedures in place to identify girls more likely to faint in advance of vaccination and to prevent the likelihood of fainting. Vaccine recipients are observed for a period of time after vaccination to identify both fainting and allergic reactions.

Anaphylaxis is a serious and potentially life threatening allergic reaction that can occur following receipt of any vaccine. Full anaphylaxis is very rare, occurring at a rate of about 1 per million vaccine recipients. Allergic events are more common, and can include hives, wheezing, and a sensation of swelling in the mouth or throat. Allergic events can be effectively treated with epinephrine and antihistamines.

Neurological events such as Guillain-Barré syndrome, a form of paralysis, are not known to be caused by this vaccine.

## 1.3 Which adverse events have been reported in BC after receipt of HPV vaccine?

In the first year of the grade 6 and 9 program for girls in BC starting September 2008, about 65 percent of 46,000 girls started their series of 3 doses of HPV vaccine. Adverse events were reported in 84 girls.

A total of 114 events were reported among these 84 recipients. Of these events reported, the most commonly reported adverse events were redness, swelling and/or pain (29%) at the injection site, rash or hives (24%), fever (15%) and allergic reactions (11%).

There were six reports of fainting with tonic-clonic movements. All recovered uneventfully. No hospitalizations following an adverse event were reported. There have been no reports of Guillain-Barré syndrome, encephalitis, transverse myelitis, autoimmune disorders or death.

A small number of reported adverse events were compatible with a flu-like illness, and could have been coincidentally associated with receipt of the vaccine because viral infections including influenza are more common in the fall and winter months, when this vaccine is given.

## 1.4 I have heard or read in the news about deaths and other serious events being reported after this vaccine. Don't these occur too?

Most reporting systems for vaccine safety include reports of events that occur after receipt of the vaccine, regardless of the likelihood that the event is caused by the vaccine. Because many millions of doses of this vaccine have been given to young women, it is not surprising that some have experienced serious health events. It is important to distinguish between an event caused by a vaccine, and an event that merely follows the receipt of a vaccine. For a vaccine like HPV, which is given in 3 doses over a 6-month period, even if recognized events are restricted to the month following vaccination, three of the 12 months in a year will have followed vaccination. Therefore, one-quarter of the illness a recipient experiences in that year will occur in a month following vaccination, regardless of whether this event is caused by the vaccine. In order to determine whether the vaccine caused the event, it is important to understand causes of such events, and to study the occurrence of these events in both those who receive and do not receive the vaccine. This is done both in clinical trials using 'control groups' of those who receive placebo or a different vaccine, and through special studies also using control groups or control periods of time, such as the period prior to vaccination.

### 1.5 Where can I find more information about HPV vaccine safety?

Information about post-marketing surveillance of safety of HPV vaccine, and about adverse events reported from throughout Canada are available from Health Canada at the following site:
http://www.phac-aspc.gc.ca/std-mts/hpv-vph/fact-faits-vacc-eng.php#1

Up to date information for the US is available at:
http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm179549.htm

### 1.6 What are the studies showing regarding the use of Gardasil™ in males?

Gardasil™ vaccine has been studied in 4,065 heterosexual and homosexual males 16-26 years of age for safety, immunogenicity, and efficacy against infection and external genital lesions (Giuliano, 2009). Currently, the per protocol results at median follow-up of 2.3 years starting with case counting beginning at month 7, show 90.4% (95% CI 69.2-98.1) efficacy for external genital lesions (warts, penile intraepithelial lesions grade 1, 2, 3) with 89.4% (95% CI 65.5-97.9) efficacy for external genital warts alone.

The vaccine was found to have a similar tolerability and safety profile as the large phase three trials in females aged 15-26 years.

In the men who have sex with men sub-study (Palefsky, 2009) the preliminary efficacy results for Gardasil™ at one year post dose three in the per protocol group was 79% (95% CI <0. - 99.6).

As the follow-up and analysis continues, additional case data will increase precision of the information. Gardasil™ is still not licensed in Canada for use in males.

### 1.7 Are there any trials for use of Gardasil™ vaccine in women over 26 years of age?

Yes, there is a Gardasil™ clinical trial in 3,819 women 24-45 years of age that is an ongoing 48 month efficacy bridging trial (Munoz, 2009). Interim 22 month results show 90.5% (CI 95% 73.7-97.5) efficacy in the per-protocol population (i.e., negative to all four HPV vaccine types at baseline to month 7) for co-primary endpoints of combined incidence of persistent infection, CIN, or external genital lesions caused by HPV 6, 11, 16, or 18 and to HPV 16/18 alone.

Efficacy results and immunogenicity are stratified for women 24-34 years and 35-45 years. Tolerability was comparable to previous clinical trials in the vaccine group, and serious adverse events were similar between vaccine and placebo groups.

### 1.8 Is there any more information about Gardasil™ vaccine duration of protection?

The duration of protection phase lV trials are ongoing in the Nordic countries (Lehtinen, 2006). To date, there is 5 year data from a phase ll trial extension (Villa, 2006). There were no cases of HPV 6/11/16/18-related precancerous cervical dysplasia or genital warts in vaccine recipients. There were six cases of HPV 6/11/16/18-related precancerous cervical dysplasia in placebo recipients (100% efficacy; 95% CI: 12–100%).

In an extended follow-up from a phase llb HPV 16 monovalent vaccine proof of concept randomised controlled trial in Seattle (Rowhani-Rahbar, 2009) the at mean 8 ½ years post vaccine efficacy was 100% for HPV 16 related CIN 1 (95% CI 43-100) and CIN 2+ (95% CI 32-100), and 96% (95% CI 73-100) for HPV 16 incident infection.

### 1.9 What is the immunogenicity of Gardasil ™ vaccine in 9 to 15 years olds versus older females?

Two immunogenicity bridging studies (Block, 2006 and Reisinger, 2007) enrolled 2,797 boys and girls 9-16 years of age for immunogenicity and safety studies. Compared to females 16-23 years, geometric mean titers one month post dose 3 were 1.7- to 2.7-fold higher in girls and boys 9 to 15 years old.

### 1.10 Is it possible that two rather than three doses of Gardasil™ vaccine would provide adequate protection?

Part 1 of the “Two versus three dose HPV vaccine study (Gardasil™)” has been completed. There were 830 subjects enrolled across Canada: 250 at the Vaccine Evaluation Centre in Vancouver at Children's Hospital/UBC. The purpose is to determine whether or not 2 doses will be as effective as 3 doses are given the exceptionally high level of antibody produced by 3 doses (especially in the younger population).

In Part 1 it was determined that almost everyone responded to the vaccine for all four HPV types in the vaccine. Five subjects had a low response to only one vaccine virus strain. The 9-13 year old girls who received only 2 doses of the vaccine developed antibody levels that were nearly twice as much as the girls in the 16-26 year age group who received 3 doses. It was also found that the 9-13 year olds who got 2 doses had almost as much antibodies as the 9-13 year olds who had 3 doses.

The study is ongoing as there is a need to be sure that these high antibody levels are going to be maintained over time. Part 2 (examination of long-term protection to 3 years) has started at all sites. The results are expected to be available mid 2011.

### 1.11 Some critics have argued that Gardasil® does not offer total protection against cervical cancer, and that other cancer causing strains of HPV may become more prevalent. Is this the case?

While it is important to collect data on changes in cervical cancer-causing HPV strains over time, this should not discourage the implementation of an effective vaccine program that can benefit women now. Gardasil® does not prevent infection from all the HPV strains that cause cervical cancer. However, it is 100 per cent effective in preventing the 2 strains (strain 16 and strain 18), which cause 70 per cent of cervical cancers in Canada. Given that there are other HPV strains that can cause cervical cancer, it is very important for women to continue with cervical screening and practice safe sex as part of a comprehensive cervical cancer prevention strategy.

### 1.12 Is serological testing for HPV antibodies available yet?

No, this is not yet available commercially in Canada. HPV DNA assays are still research tests and are not available for clinical management.

Even if there was a serological test for HPV antibodies, it is important to acknowledge that some women may have undetectable antibody levels that may be sufficient to offer protection against future genital HPV infection.

## 2.0 THE HPV VACCINE PROGRAM

### 2.1 What were the key results from the study led by Dr. Gina Ogilvie, entitled "Parental Factors Associated with Uptake of HPV Vaccine: A Population Based Provincial Evaluation?"

The study was undertaken to report on the uptake level of the first dose of the HPV vaccine and to determine parental factors associated with receipt of the HPV vaccine. All parents of girls enrolled in Grade 6 during the academic year of September 2008 – June 2009 were eligible to participate. Eligible households identified through the integrated public health information system (iPHIS) were randomly selected and those who consented completed a validated survey exploring decisions around HPV vaccine receipt as well as factors associated with vaccine uptake.

Between January 18, 2009 and March 19, 2009, 2,025 parents agreed to complete the survey. 65.1% of parents in the survey reported that their daughters received the first dose of the HPV vaccine.

In the same school based vaccine program, 1790 (88.4%) consented to the hepatitis B vaccine, and 1751 (86.5%) consented to meningococcal C vaccine.

The main reasons for having daughters receive the HPV vaccine were:
- the effectiveness of the vaccine (47.9%)
- advice from a physician (8.7%)
- concerns about daughter's health (8.4%).

The main reasons for not having a daughter receive the HPV vaccine were:
- concerns about HPV vaccine safety (29.2%)
- preference to wait until daughter is older (15.6%)
- not enough information to make an informed decision (12.6%).

In multivariate analysis, overall attitudes to vaccines, impact of the HPV vaccine on sexual practices and childhood vaccine history were predictive of parents having daughters receive the HPV vaccine. In contrast, having a family with two parents, having three or more children and having more education was associated with a decreased likelihood of having daughter receive the HPV vaccine.

To maximize uptake of the HPV vaccine, these findings have important implications:
- Continue to focus on the efficacy and the overall benefits of the vaccine in preventing cervical and HPV related cancers and the seriousness of cervical cancer/HPV diseases in messaging
- Continue to partner with practitioners, particularly physicians, to ensure they possess accurate information about the HPV vaccine including its safety profile
- Highlight that youth sexual health practices have improved according to the McCreary Report over the past ten years since the commencement of the hepatitis B vaccine program and other evidence indicating that education about sexuality is associated with reduced sexual risk taking behaviour
- Focus on the advantages, opportunities and benefits of early over late vaccination

### 2.2 What promotional efforts are planned for the second year of the HPV program?

The focus of promotion will be physician education. The results from the Ogilvie et al. (2009) study identified the need to look for ways to provide educational support to BC physicians about the benefits of HPV vaccine. Efforts will focus on three major areas:

(i) Helping coordinate and organize Continuing Medical Education (CMEs) sessions for General Practitioners throughout the province.

(ii) Working with the provincial Family Practitioners Oncology (FPO) Network of BC to explore ways in which they may contribute as HPV vaccine advocates in BC. This group's involvement is key because of their knowledge in two areas.

More so than other types of physicians, FPOs are typically the most familiar with the science behind the HPV vaccine and able to promote it. Secondly, as Family Practitioners, they are more likely to have seen first hand, through both the morbidity and mortality of their patients, the effects of this disease on individuals and their families. It is this unique combination of “stories and science” that make Family Practitioners in Oncology uniquely qualified and credible witnesses as to why the HPV vaccine is so important when it comes to preventing future cases of the disease.

This work will first involve surveying the FPO group with a series of options/opportunities as to how they might see themselves being utilized in HPV education to others. These options may involve either helping to educate other health care workers such as their physician peers or exploring ways to help educate the general public in their local area (e.g., working with local parent groups, or being available to speak to local media endorsing the vaccine). A major goal of this effort will be to help facilitate more formalized links between the Family Practice Oncologists within a particular geographic area and other health workers within the same area who also deal with questions about the HPV vaccine.

(iii) Looking for opportunities to provide written pieces to physician journals, newsletters, and bulletins in BC to advocate for the vaccine.

### 2.3 Some parents are concerned that receipt of HPV vaccine will result in earlier or increased sexual activity as the girls think they are protected by the vaccine. What can we tell these parents?

Since 1992, BC has had a hepatitis B vaccine program for eleven year old girls and boys. In the commensurate time period, the McCreary Report, our provincial adolescent health survey, has reported an improvement in sexual practices in adolescents, with delayed sexual debut, as well as safer sexual practices. This is despite the availability of a vaccine for a sexually transmitted infection in a publicly funded school program in the province. This information should be shared with parents so that they are aware there is provincial data showing that use of a vaccine for a sexually transmitted infection does not increase risky sexual behaviour. Moreover, there are many factors that influence young peoples’ decisions about early sexual activity. These include peer pressure, self-image, sex education, and impact of the media. There is no evidence that being vaccinated against HPV influences a young girl’s decision regarding earlier or increased sexual activity.

### 2.4 Why are we not immunizing high-risk populations (e.g., youth attending youth clinics, women in correctional facilities)?

The goal of the program is to maximize benefits for the population. The Canadian cost-effectiveness analysis that was done before the start of the program determined the most cost-efficient approach was a school-based program.

The funding that was allotted from the federal government has been used to provide vaccine to those most likely to benefit (i.e., the younger age groups most of whom are pre-sexual debut).

### 2.5 What if a student missed HPV vaccination in grade 6 or grade 9?

Anyone in grade 6 or 9 remains eligible for the vaccine in the future. In subsequent years eligibility will be based on the birth year of 1997 for female grade 6 students and 1994 for female grade 9 students.

However, these girls will most likely be immunized in the health unit and not in school. This is not as efficient an approach to program delivery as is a school-based program. More importantly, the objective of the HPV vaccine program is to protect girls at a younger age, preferably in grade 6, for the following reasons:

- They mount a better immune response. As discussed in Question 1.9, geometric mean titers one month after dose 3 were 1.7 to 2.7 times higher in girls 9 to 15 years old compared to females 16-23 years old.
- More of the younger girls are not yet sexually active, so immunity will be gained before exposure to the virus.
- The grade 9 program is a catch-up and sunsets in June 2011. Girls in grade 6 that do not receive the vaccine in school will not be offered the vaccine in a school-based grade 9 program.

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