



HPV Questions and Answers
Issue #2
August 1, 2008

Table of Contents

1.0	HUMAN PAPILLOMAVIRUS (HPV) INFECTION.....	1
1.1	Where does the human papillomavirus virus live on the human body?	1
1.2	How long does the human papillomavirus live on various surfaces?.....	1
1.3	What is the natural history of HPV infection in males?.....	1
1.4	What are the risk factors for HPV infection in males?	1
1.5	Does HPV infection cause cancer in males?.....	1
1.6	If over 95% - 99% of cervical cancers are associated with certain types of HPV, then what causes the 1 - 5 % of other cases of cervical cancer?	2
1.7	Why do some precancerous cervical lesions progress more rapidly in some females?.	2
1.8	Can HPV infection be treated?	2
1.9	What about media reports claiming HPV infection does not cause cervical cancer?	2
1.10	Can you be re-infected by the same HPV strain more than once?	3
1.11	Are plantar warts caused by HPV strains and is there any chance of spreading plantar warts to the genital areas?	3
1.12	What are the survival rates for someone diagnosed with cervical cancer?	3
2.0	HPV VACCINE	4
2.1	Is a second HPV vaccine licensed yet in Canada?	4
2.2	Anaphylactic reaction to yeast is listed as a contraindication to receipt of Gardasil™. What about Celiac disease – is that a contraindication?	4
2.3	Pregnancy is also listed as a contraindication to Gardasil™. Is there a need to screen for pregnancy prior to each immunization?	4
2.4	The media is often quoting data from VAERS. What is VAERS and what does it do?	4
2.5	There have been VAERS reports of fainting following HPV vaccine. Is there reason for concern?	5
2.6	What adverse events following immunization with Gardasil have been reported in Canada?	6
2.7	Can GARDASIL be given to women >26 years of age or is it still only licensed for females ≥ 9 years to ≤ 26 years?	6
2.8	Is serological testing for HPV antibodies available yet?.....	6
2.9	Will girls/women be protected against HPV and related diseases, even if they don't get all three doses?	6
2.10	How long has Gardasil been used in other countries?	7
2.11	How long has Gardasil been studied?	7
3.0	ERRATUM TO HPV Q & A #1 (DATED FEBRUARY 29, 2008)	8
4.0	REFERENCES	9



1.0 HUMAN PAPILLOMAVIRUS (HPV) INFECTION

1.1 Where does the human papillomavirus virus live on the human body?

The virus is ubiquitous: it can live on all skin surfaces. Of the more than 100 types of HPV that can infect many parts of the body, at least 40 HPV types are able to infect the genital tract. The virus lives over the entire genital region. That is why anyone (females and males) who has any kind of skin to skin genital contact with an infected person can get HPV – intercourse isn't necessary.

Condoms can offer some protection from HPV. However, this virus can be present on skin that is not covered by the condom and can then spread with skin-to-skin contact.

1.2 How long does the human papillomavirus live on various surfaces?

There is no data on this topic.

1.3 What is the natural history of HPV infection in males?

Virtually ALL of the natural history data on HPV relates to cervical infections in **women**. There is very little information on men. So, whenever acquisition, persistence and clearance are discussed, the numbers relate only to women. For example, the estimate of 90% clearance is for women; 70% risk of acquisition is also for women, not for men.

1.4 What are the risk factors for HPV infection in males?

The risk factors for HPV infection in males have not been studied to the extent of those in females. An increasing number of previous sexual partners in the male have been identified as a risk, both lifetime as well as recent partners, and smoking. Condom use was protective. Being uncircumcised was also found to be a risk in some studies.

With regard to the circumcision issue, data is conflicting and more information is needed. In general, circumcision has proved to be preventive (as opposed to increasing risk) for any acquisition of a sexually transmitted infection. This is likely because the relatively fragile skin below the foreskin becomes less fragile in a circumcised male, and so less vulnerable to infection. During an erection, the fragile epithelium below the foreskin is unprotected and thus at risk for infection from any sexually transmitted infection, including HPV. It is still unknown if circumcision is protective or not. This is an area of research pertaining to HPV infection in men.

1.5 Does HPV infection cause cancer in males?

HPV has been associated with cancers of the penis and anus in which mechanisms of oncogenicity are presumed to be similar to those of the cervix. However, they have not yet been identified as the cause of these cancers, as they have for cervical cancer in women.



1.6 If over 95% - 99% of cervical cancers are associated with certain types of HPV, then what causes the 1 - 5 % of other cases of cervical cancer?

Most of the scientific community agrees that 99% of cervical cancers are associated with certain types of HPV. The remaining 1-% of cervical cancers is likely due to HPV that is not yet typed.

1.7 Why do some precancerous cervical lesions progress more rapidly in some females?

The time it takes for an infection to progress to invasive cervical cancer varies widely. In young women, low-grade lesions often disappear spontaneously. A typical progression to high-grade lesions takes 10 years or longer, but cancer develops more quickly in some women. In very rare cases, lesions have been reported to progress to invasive cancer in less than one year.

The reasons for this variation are not fully understood. The virulence of the HPV subtype, and the woman's immunity, genetic make-up and genetic predisposition to developing cancer all play a role.

The vast majority of precancerous lesions, which progress slowly, can be detected with regular screening and be treated. Cervical cancer can also be more effectively treated when detected early.

1.8 Can HPV infection be treated?

There is no cure for HPV infection, but there are treatments for the health problems that HPV can cause, such as genital warts, cervical cell changes, and cancers caused by HPV. Regular screening with a Pap test can find cervical cell changes before cancer develops.

1.9 What about media reports claiming HPV infection does not cause cervical cancer?

No human cancer has been shown to be caused by a single agent, in the same way that cervical cancer is caused by HPV. The association between HPV and cervical cancer is very strong – stronger than the association between smoking and lung cancer, and stronger than the association between alcohol and oral cancer.

In 1995, in its comprehensive review of studies evaluating the carcinogenic risks of HPV to humans, the World Health Organization (WHO) International Agency for Research on Cancer (IARC) classified HPV types 16 and 18 as carcinogenic to humans. The following was stated in their document: "...strong associations with HPV-16 DNA have been observed with remarkable consistency for invasive cancer and high grade Cervical Intraepithelial Neoplasia (CIN), ruling out the possibility that this association can be explained by chance, bias or confounding factors...After HPV-16, HPV -18 is the type most clearly shown by epidemiological data to be a human carcinogen."



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

Since the WHO's IARC 1995 report, scores of research studies published in peer reviewed journals have continued to confirm the role of HPV as the cause of cervical cancer.

In its most recent monograph of 2005, the IARC stated "The new epidemiological data reviewed in the present volume strongly support and further confirm the previous evaluation of types 16 and 18 and provide new evidence for other HPVs. This information, which includes strong evidence of carcinogenicity at sites other than the cervix, supports new evaluation for other HPV types."

1.10 Can you be re-infected by the same HPV strain more than once?

The evidence on this is not definitive. According to the Society of Gynecologists and Obstetricians of Canada, most women (80%) who become infected with a specific HPV type will later show no evidence of that type and it is generally thought that subsequent re-infection with the same type is uncommon.

1.11 Are plantar warts caused by HPV strains and is there any chance of spreading plantar warts to the genital areas?

Plantar warts are caused by human papillomavirus, but by different subtypes. The subtypes that cause plantar warts tend to preferentially infect the soles of the feet, and thrive in moist, warm environments such as pool decks.

1.12 What are the survival rates for someone diagnosed with cervical cancer?

Based on information posted on the BC Cancer Agency website, there is approximately a 90% survival rate at 1 year, 80% at 3 years and approximately 78% at 5 years.



2.0 HPV VACCINE

2.1 Is a second HPV vaccine licensed yet in Canada?

A second vaccine, Cervarix (manufactured by Glaxo Smith Kline), was originally expected to be approved by Health Canada in April 2008. It is not yet licensed in Canada. It will protect against HPV types 16 and 18.

2.2 Anaphylactic reaction to yeast is listed as a contraindication to receipt of Gardasil™. What about Celiac disease – is that a contraindication?

Celiac disease is not a contraindication for receipt of Gardasil™ vaccine.

2.3 Pregnancy is also listed as a contraindication to Gardasil™. Is there a need to screen for pregnancy prior to each immunization?

No, there is no expectation to do so. During the course of the Phase III studies with Gardasil™ there were 1,115 subjects who became pregnant in the vaccine group and 1,151 in the placebo group. Pregnancy was an exclusion criterion for entering the trial, but these women were found to be pregnant during the study. Further vaccination was delayed until completion of the pregnancy. The proportion of spontaneous abortion was similar in both groups (26%). Congenital anomalies were noted in 15 of the vaccine group and 16 in the placebo group. None were considered to be related to the vaccine. These rates of congenital anomalies were the same as in surveillance registries.

Although the vaccine has not been causally associated with adverse outcomes of pregnancy or adverse events to the developing fetus, the data on vaccination in pregnancy are limited. Until further information is available, Gardasil™ vaccine is not recommended for use in pregnancy. Initiation of the vaccine series should be delayed until after completion of the pregnancy. If a woman is found to be pregnant after initiating the vaccination series, completion of the three-dose regimen should be delayed until after pregnancy. If a vaccine dose has been administered during pregnancy, there is no indication for any intervention.

2.4 The media is often quoting data from VAERS. What is VAERS and what does it do?

The [Vaccine Adverse Event Reporting System \(VAERS\)](#) is a national passive reporting system in the United States. It was set up by the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) as a post-marketing vaccine safety surveillance program. It collects information about adverse events that occur after the administration of US licensed vaccines.



While VAERS provides useful information on vaccine safety, the data are somewhat limited. Specifically, any event after vaccination can be reported, with no restriction on the interval between vaccination and the onset of the event and no requirement for medical care having been rendered. Anyone can submit a report, including health care professionals, pharmaceutical companies, parents and patients. The VAERS is essentially for hypothesis generating and not hypothesis testing. For the most up-to-date VAERS information on adverse events following immunization with Gardasil, go to: <http://www.cdc.gov/vaccinesafety/vaers/gardasil.htm>

2.5 There have been VAERS reports of fainting following HPV vaccine. Is there reason for concern?

Since 2005, VAERS has detected a trend of increasing fainting or syncope reports. VAERS received 463 syncope reports during January 1, 2005 – July 31, 2007, compared with 203 during January 1, 2002 – December 31, 2004. This increase coincides with the licensure and recommendation of three vaccines for adolescents: meningococcal quadrivalent conjugate vaccine (MCV4), tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap), and human papillomavirus (HPV) vaccine.

Among post-vaccination syncope reports in persons aged ≥ 5 years, 49% were adolescent females aged 11 to 18 years. At least one of the three adolescent vaccines (HPV, MCV4, and Tdap) was received in 60% of reports involving a single vaccine; HPV was the most frequently reported associated vaccine type (52% of single vaccine reports).

Among the 41 syncope reports with secondary injuries and information about the timing of syncope, 76% occurred in adolescents aged 11 to 18 years. The time from vaccination to syncope onset was less than 5 minutes in 49%, and less than 15 minutes in 80% of the reports. Ten of the 41 (24%) sustained injuries that were classified as serious in nature.

It is not known whether specific vaccines cause syncope. Nearly all vaccines have been reported to be associated with post-vaccination syncope. It is not known how common syncope is and there are no published studies on the rate of syncope after vaccination. Incidence rates based on VAERS data cannot be calculated because of VAERS limitations such as lack of data on the number of vaccine doses administered.

Further research comparing the age-specific incidence rate of syncope after an individual vaccine would help answer the question.



2.6 What adverse events following immunization with Gardasil have been reported in Canada?

As of June 30, 2008 the Public Health Agency of Canada received a total of 212 reports of adverse events. These reports are mostly of minor adverse events, including injection site reactions, which are consistent with the results reported by clinical trials conducted prior to the approval of the vaccine, and can be expected with the administration of any vaccine. There were no reports of death or Guillain-Barré syndrome (GBS).

Six hospitalizations following HPV immunization have been reported to date in Canada. One of these was found to be possibly related to the vaccine, and another is pending scientific review. The other four hospitalizations were not found to be directly related to the vaccine.

The reporting rate for adverse events for Gardasil in Canada is 36.6 per 100,000 doses distributed. This is comparable to the rate of reported adverse events for all vaccines in Canada, which has varied between 16 to 40 per 100,000 doses over the period 1992-2004.

2.7 Can GARDASIL be given to women >26 years of age or is it still only licensed for females ≥ 9 years to ≤ 26 years?

The vaccine is not licensed for those > 26 years of age. Studies are ongoing and recent data published has shown the vaccine is effective in the age group of 26 – 45 years. On an individual level, a clinician could make the decision to immunize a woman over the age of 26 years. This would currently be “off-label use.”

2.8 Is serological testing for HPV antibodies available yet?

No, this is not available commercially. HPV DNA assays are still research tests and are not available for clinical management. The BC Centre for Disease Control is working on a type specific HPV DNA assay, but that will likely still be a research assay.

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.

2.9 Will girls/women be protected against HPV and related diseases, even if they don't get all three doses?

Studies are underway at the Vaccine Evaluation Centre (Children's and Women's Hospital, Vancouver) to determine whether two doses of the vaccine offer the same level of protection as three doses. Until we know the results, it is very important for females to get all three doses of the vaccine as there is currently no evidence of efficacy with a two dose HPV vaccine schedule.



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

2.10 How long has Gardasil been used in other countries?

Since 2006, Gardasil has been licensed/approved in 103 countries. More than 26 million doses have been distributed worldwide, including nearly 16 million in the United States. It is estimated that 8 million girls and women have received the vaccine in the United States since June 2006.

2.11 How long has Gardasil been studied?

Published results from pre-clinical studies in animals began in 1995. The earliest phase II safety and efficacy studies in humans with the monovalent formulation (HPV 16) started in 1998 and the large phase III trials started in 2002.

The following reference provides a published summary of the clinical development program for Gardasil: Barr, E. & Tamms, G. (2007). Quadrivalent human papillomavirus. *Clinical Infectious Diseases*. 45: 609 – 617.



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

3.0 ERRATUM TO HPV Q & A #1 (DATED FEBRUARY 29, 2008)

Question 2.11: Is there testing available to determine if the vaccine will be effective in sexually active women?

The wording of the answer to this question has been clarified as follows:

There are two methods of looking for evidence of an HPV infection. One is a test at the cervix that is performed like a Pap smear, using molecular techniques to study the specimen. This will determine if a woman currently has a cervical HPV infection. The other method is looking for presence of antibodies to HPV in the blood, to determine if a woman has previously been infected with HPV.

Cervical testing for HPV provides evidence of current HPV infection, but does not offer any information about prior HPV infections. It also does not provide any information regarding an immune response to a previous HPV infection. Testing for cervical HPV infections is not currently performed routinely in British Columbia. Testing for antibodies to HPV is not available commercially, and is done only in research settings at this time.



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

4.0 REFERENCES

Barr, E. & Tamms, G. (2007). Quadrivalent human papillomavirus. *Clinical Infectious Diseases*, 45:609 – 617.

Department of Health and Human Services Centers for Disease Control and Prevention. Vaccine Adverse Event Reporting System (VAERS). Available at: <http://www.cdc.gov/vaccinesafety/vaers/>

Koutsky, L.A., Ault K.A., Wheeler CM et al. (2002). A controlled trial of a human papillomavirus type 16 vaccine. *N Engl J Med*, 347:1645-51.

Public Health Agency of Canada. (2007). Statement on human papillomavirus vaccine. *Canada Communicable Disease Report*, 33 - ACS-2:1-32. Available at: <http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/07pdf/acs33-02.pdf>

Public Health Agency of Canada. (2008). The FACTS on the Safety and Effectiveness of HPV Vaccine. Available at: http://www.phac-aspc.gc.ca/std-mts/hpv-vph/fact-faits_e.html#4

World Health Organization International Agency for Research on Cancer. (2007). Human papillomavirus. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Volume 90.