



A PHARMACY CONTINUING EDUCATION PROGRAM

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May 2009 "Prevention of HPV Infections" #707-000-09-005-H01-P



THIS MONTH  
"Prevention of HPV  
Infections"

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The FDA-approval of Gardasil™ in 2006 has brought more attention to HPV-associated infections & diseases. It's always gratifying when we can bring "new & up-to-date" info to you that can be shared with patients. It has been shown that this topic is raising tremendous numbers of questions from the public. That is why we have decided to focus on this area in this lesson. The goals are to review the disease, and discuss the vaccine. A lot of technical information is presented. Don't get "hung up" on that. The major concern is RESULTS indicated by testing of the vaccine (positive outcome for patients). This lesson provides 1.25 hours (0.125 CEUs) of credit, and is intended for pharmacists in all practice settings. **The program ID # for this lesson is 707-000-09-005-H01-P. Pharmacists completing this lesson by May 31, 2012 may receive full credit.**

**To obtain continuing education credit for this lesson**, you must answer the questions on the quiz (70% correct required), and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. Computerized records are maintained for each participant.

If you have any comments, suggestions or questions, contact us at the above address, or call toll free 1-800-323-4305. (In Alaska and Hawaii phone 1-847-945-8050). **Please write your ID Number (the number that is on the top of the mailing label) in the indicated space on the quiz page** (for continuous participants only).

**The objectives of this lesson are such that upon completion the participant will be able to:**

1. Discuss the epidemiology of HPV infection in the U.S.
2. Describe the natural history & clinical sequelae of HPV infection.
3. List the treatment & prevention options for HPV infection.
4. Comment upon the indications, efficacy & economic impact of the quadrivalent HPV vaccine.

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## AN UPDATE ON PREVENTION OF HPV INFECTIONS

Genital human papillomavirus (HPV) is the most common sexually transmitted disease in the United States. It is estimated that 6.2 million persons are infected each year of which the majority of the infections are self-limiting. Persistent genital HPV infection can cause cervical cancer in women and many types of anogenital cancers and genital warts in both men and women. (1) It is estimated by the American Cancer Society that over 11,000 cases of invasive cervical cancer were diagnosed in the 2008. (2) The approval of the Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant (GARDASIL™) in 2006 has brought more attention to prevention of HPV-associated infections and diseases. That is the focus of this lesson.

### HPV: THE BIOLOGY BASICS

The HPVs are nonenveloped, double-stranded DNA viruses in the family of *Papillomaviridae*. (1) Isolates of HPV are classified as types and numbers based on their order of discovery. All HPVs are enclosed in a capsid shell composed of the major and minor capsid proteins L1 and L2, respectively. The functions of these proteins vary. The purified L1 protein will self-assemble to form empty shells that resemble a virus, called virus-like particles (VLPs). In addition to the structural genes (L1 and L2), the genome encodes several early genes (E1, E2, E4, E5, E6, and E7) that enable viral transcription and replication and interact with the host genome. E6 and E7 proteins from high-risk types are the primary oncoproteins that manipulate cell cycle regulators, induce chromosomal abnormalities, and block apoptosis (programmed cell death). (1)

HPV initiates infection in the basal layer of the epithelium. The viral genome amplification occurs in differentiating cells using the cellular replication machinery. In epithelium cells that are normally non-dividing, the HPV keeps the cell in an active cell cycle. This results in a thickened, epithelial lesion. With neoplastic progression, the virus may integrate into the host chromosomes.

### HPV: THE IMMUNOLOGY BASICS

Because HPV infections are restricted to the epithelium, they can evade the host immune response. Humoral and cellular immune responses have been documented, but the correlation to immunity have not been established. The clinical significance of the immune response is not well understood, but neutralizing antibodies are produced; they not only protect against infection but also are associated with lesion resolution. (3) In one study, only 54- 69% of women with HPV 6, 16, or 18 infections had antibodies. The median time to seroconversion in newly infected women is approximately 8 months. (1)

### HPV: LABORATORY TESTING

HPV cannot be cultured; detecting HPV requires identification of the genetic material (i.e. DNA ). Detection will be impacted by the anatomic region and the method of specimen collection. The Digene Hybrid Capture® 2 High-Risk HPV DNA (HC2) test is approved by the U.S. Food and Drug Administration for clinical use in women with equivocal Papanicolaou (Pap) test results (i.e. atypical squamous cells in undetermined significance (ASC-US) ) and in combination with the Pap test for cervical cancer screening in women aged > 30 years. This test is not approved for use in men. This test detects 13 high-risk types of HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68), but the results are reported as positive or negative, not type-specific. In research studies, nucleic acid amplification methods can be employed that identify the HPV type and quantitative results. In addition, serologic assays to detect antibodies to the L1 viral protein are available for research studies, but these are not standardized. (1)

## EPIDEMIOLOGY OF HPV INFECTION TRANSMISSION AND RISK FACTORS

Genital HPV is transmitted by genital contact through sexual intercourse. The most consistent predictor of infection has been measure of sexual activity, specifically the number of sex partners (lifetime and recent) in women. As the number of lifetime sex partners increases, the rates of HPV infection increase. One study has indicated that 14.3% of women aged 18-25 years with one lifetime partner had HPV infection, whereas, 22.3% of women with two lifetime partners and 31.5% with more than three lifetime partners had HPV infections. HPV transmission can occur with non-penetrative intercourse, but this is less common. Nonsexual transmission routes of genital HPV include mother to a newborn baby (vertical transmission), but this is uncommon. (1)

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The transmission of HPV is less understood in males. The risks factors include: increased age, number of sexual partners, and history of sexually transmitted diseases. There is conflicting data about whether circumcision is protective against HPV infection. (4) Overall the data in HPV infections in males are less consistent due to variation in specimen collection and testing procedures. (1)

### **NATURAL HISTORY OF HPV INFECTION**

The majority of HPV infections are transient, asymptomatic, and cause no clinical problems. Estimates suggest that 70% of new HPV infections clear within 1 year, and up to 90% clear infection within 2 years. Persistent infection with high-risk types of HPV is the most important risk factor for precancerous lesions and invasive cervical cancer.

The persistence and progression to cancer are dependent on host factors (immune status, etc) and the HPV type. Certain HPV types are more oncogenic than others, of which HPV 16 is the most oncogenic among other high-risk HPV types. Other factors associated with cervical cancer include cigarette smoking, increased parity, increased age, other sexually transmitted infections, immune suppression, long-term oral contraceptive use and other host factors. The time period between initial infection of HPV and the development of cervical cancer is usually decades. There are many aspects of the pathogenesis of HPV infection that are not well understood. (1)

In men, the majority of HPV infections are asymptomatic, but some can lead to cancer as well. Risk factors for acquisition of HPV are similar and include cigarette smoking, greater number of female sex partners, and decreased condom use. (5) The natural history of the infection and epidemiology is less understood in males, but more research is being conducted.

Human immunodeficiency virus (HIV)-seropositive men who have sex with men (MSM) are at higher risk of human papillomavirus (HPV) infection with HPV 6 and 16.(6)

### **HPV PREVALENCE AND INCIDENCE**

In the United States, an estimated 6.2 million new HPV infections occur every year among persons aged 14 to 44 years, of which 74% occur in those aged 15-24 years.

Prevalence and incidence data are obtained from family planning and sexually transmitted disease clinics or university based clinics, so these estimates may not be representative of the whole population. These studies report the prevalence of HPV DNA ranges from 14% to 90%. The prevalence was highest among sexually active females aged < 25 years, and the prevalence decreases with increasing age.

In two population based studies, the prevalence of HPV (any type) in women aged 18 to 25 years old was 26.9%. When the prevalence of HPV types was examined, types 16 or 18 occurred in 7.8%, and types 6 or 11 occurred in 2.2% in the study population. (1)

Less prevalence data is available in heterosexual men due to a poor understanding of which sites should be tested. It is estimated the prevalence ranges from 1.3 to 72.9% when multiple anatomic sites or specimens were evaluated. (1,7)

### **CLINICAL SEQUELAE**

The clinical sequelae of HPV infection can result in cancer precursors (anogenital lesion and cervical lesions) to cervical and anogenital cancers. In addition, HPV infections can lead to anogenital warts and respiratory papillomatosis. It is estimated in the United States that 75% of cervical cancers are squamous cell, with the remaining being adenocarcinomas. HPV 16 and 18 are responsible for 68% of the squamous cell carcinomas and 83% of adenocarcinomas. See Table 1 (1)

Cervical HPV Infection can result in histologic changes that categorize as cervical intraepithelial neoplasias (CIN) grades 1, 2, 3 which are based on the degree of abnormality in the cervical epithelium. The majority of CIN1 clear spontaneously, with only 1% progressing to cancer. With CIN2 and CIN3, the rate of clearance is approximately 30% to 40%, and a higher percentage can progress to cancer if left untreated. Cervical cancer screening with the Pap test can detect cytologic changes, but the results can be ambiguous. The abnormalities detected include ASC-US (atypical glandular cells), LSIL, HSIL (low-grade and high-grade squamous intraepithelial lesions) and AIS (Adenocarcinoma in situ). HPV 16 and 18 are commonly associated with high grade lesions. (1)

### **VAGINAL AND VULVAR CANCER**

Unlike cervical cancer, HPV is not associated with all vaginal and vulvar cancers, but the majority of vaginal cancer and vaginal intraepithelial neoplasias (VaIN) are; HPV 16 is the most common type. Vaginal cancer is rare; only 1070 cases were found in 2003 in the United States. No routine screening exists in the United States for vulvar and vaginal cancers. (1)

HPV is associated with approximately half of the vulvar squamous cell cancers. HPV-associated vulvar cancer occurs in younger women and is preceded by vulvar intraepithelial neoplasia (VIN).

### **ANAL CANCER**

Ninety percent of anal squamous cell cancers are associated with HPV. Anal cancer is more common in women than men. It is estimated that 5070 new cases were diagnosed in 2008, 60% in women. (8) Men who sleep with men and HIV positive patients are at high risk for anal cancer, but currently there are no standardized screening guidelines for these populations.

### **GENTIAL WARTS**

Anogenital warts are caused by HPV, of which 90% are caused by HPV 6 and 11. After infection, it takes approximately 2-3 months to develop anogenital warts, but not all patients develop warts. Of those that develop warts, up to 30% regress spontaneously. Recurrence is common in 30% of patients despite spontaneous regression or treatment. (1)

### **RECURRENT RESPIRATORY PAPILLOMATOSIS**

Recurrent Respiratory Papillomatosis (RRP) is caused by low-risk HPV types such as 6 or 11, and it can result in recurrent warts or papillomas in the upper respiratory tract. Based on the age of onset, RRP can be categorized as either juvenile onset (< 18 years of age) or adult onset. Juvenile onset is thought to be a result of vertical transmission from the mother to the baby during delivery. The epidemiology and disease course of adult onset RRP is not well understood. (1)

### **TREATMENT OF HPV INFECTION**

HPV infections are not treated; rather the treatment is directed toward the HPV-lesions. The treatment options for genital warts, cervical, vaginal and vulvar cancers range from cryotherapy, electrocautery, laser therapy, and surgical excision. Genital warts can be treated with topical pharmacologic agents.

### **PREVENTION**

Some evidence suggests that health-education programs and condom use reduce the risk of cervical cancer at a population level. Condoms may reduce the risk of HPV-associated infections, but is not 100% effective because condoms do not cover all affected areas, such as the male anogenital skin.(9) In college-aged women, there was 70% reduction in new HPV infections (both high-risk and low-risk HPV types) when condoms were used consistently, compared to the group that used condoms less frequently. (10)

Neither routine surveillance nor partner notification is conducted for HPV prevention because it is so prevalent that the majority of the partners of persons found to have HPV infections are already infected. (1)

### **CERVICAL CANCER SCREENING**

The death rates attributable to cervical cancer have significantly declined since the 1950s due to increased screening, mainly by the Pap test. The Pap test can detect precancerous changes in the cervix prior to the cancer developing and identify cancers in the curable stages. The death rate due to cervical cancer continues to decline by 4% every year. (2)

Pap test screening includes either the conventional Pap or liquid-based cytology. Several professional organizations have published guidelines to direct the frequency of Pap test in certain age groups. See Table 2

It is estimated in the United States that 82% of women have had a Pap test within the last three years. Certain populations continue to have lower screening rates especially in women with less than a high school education, women without health insurance, foreign-born women and certain ethnic groups (Hispanics and Asians). In one study conducted from 1995 to 2000, it was approximated that 56% of women diagnosed with invasive cervical cancer failed to have Pap tests during the preceding 3 years. (11)

Despite these prevention measures, there continues to be over 11,000 cases of invasive cervical cancer diagnosed in the United States. Worldwide, cervical cancer remains a leading cause of death in women; half a million women are newly diagnosed with cervical cancer, with a quarter of a million deaths each year. With these statistics, it is no wonder that there is much excitement and controversy about the advent of the HPV vaccine. (12)

### **THE HPV VACCINE**

The US Food and Drug Administration licensed the quadrivalent HPV vaccine (GARDASIL™) produced by Merck & Co for the prevention of HPV infection in women 9 to 26 years of age in 2006.

### **HPV VACCINE: COMPONENTS**

The quadrivalent HPV vaccine (QHV) is a non-infectious recombinant quadrivalent vaccine created from purified virus-like particles (VLP) of the capsid protein (L1) of the HPV types 6, 11, 16, and 18. The L1 proteins are produced in a separate recombinant process using *Saccharomyces cerevisiae* which self-assemble into VLPs. The VLPs are attached to an aluminum adjuvant. The QHV does not contain any thimerosal or antibiotics. (13)

## DOSE AND ADMINISTRATION

QHV is administered as an intramuscular injection as three separate 0.5mL doses. The second dose should be given 2 months after the first dose, and the third dose 6 months after the first dose. It is available as a sterile suspension, as a single dose vial or as a prefilled syringe.

## QHV: EFFICACY DATA

There have been four randomized-double blind, placebo-controlled studies evaluating the efficacy of the HPV vaccine. The studies were designed to evaluate pre-defined endpoints evaluating the prevention of HPV related infection and disease in women aged 16 to 23. The phase 2 studies were proof-of-concept trials that investigated the HPV monovalent (protocol 005) and HPV quadrivalent (protocol 007) vaccines using persistent infection as an endpoint. The phase 3 studies (protocol 013, 015) evaluated the efficacy of the quadrivalent vaccine on clinical lesions. These studies were combined to improve the precision of the findings. Various endpoints were assessed in each study, including vaccine-type related persistent infection, CIN, VIN, and VaIN and genital warts. (13)

### PHASE 2 STUDIES (PROTOCOL 005 AND PROTOCOL 007)

The two phase 2 studies evaluated persistent infection, defined as a vaccine HPV type detected by PCR at two or more consecutive visits four months apart or the last visit if lost to follow up. The monovalent vaccine was administered to over 2,000 women aged 16 to 23 years of age. The participants were given 3 doses of the HPV-16 vaccine or placebo. The efficacy of monovalent vaccine in protocol 005 was 100% against persistent HPV infection at the midpoint (17.4 months), and 94% at the end of the study (3.5 years). (14) A follow-up study indicated 100% protection against HPV-16 related CIN 2 or 3 after the administration of the HPV-16 vaccine.

Protocol 007 evaluated the QHV, containing HPV-6, HPV-11, HPV-16 and HPV-18, in over 1,000 females aged 16 to 23 years old. Participants were randomized to either vaccine or placebo, given as 3 doses, and were assessed for persistence infection with HPV 6, 11, 16, and 18 for up to 36 months after vaccine administration. The efficacy of the primary endpoint was found to be 89.5% (95% confidence interval [CI] = 70.7%-97.3%,  $p < 0.001$ ) in the vaccinated group compared to the placebo. (15)

The analysis from the study established the vaccine dosage used in the phase 3 trials.

### PHASE 3 TRIALS

Two phase 3 studies (protocol 0013, protocol 015) were completed to assess the safety and efficacy of the QHV in females. The composite endpoints were occurrence of genital warts, vulvar, or vaginal intraepithelial neoplasia or adenocarcinoma in situ, or cancer associated with HPV types 6, 11, 16, or 18.

Protocol 015 included 12,157 women aged 16 to 26 years from over 90 study sites in 13 countries. The participants were followed up for an average of 3 years after vaccine administration. The composite endpoints were assessed with a Pap test, cervicovaginal sampling for HPV DNA testing, and detailed genital exam at day 1, and months 7, 12, 24, 36 and 48. In the per-protocol population, defined as participants who completed the vaccination regimen, did not violate the protocol, were seronegative, and had negative findings on polymerase chain reaction (PCR) for HPV strains in the vaccine through 1 month after the third vaccine dose, the efficacy against CIN 2 or 3 or AIS was 98% (95% CI, 86% to 100%). (1,13)

Protocol 013 evaluated the safety and efficacy of the QHV in 5422 females aged 16 to 23 years of age from 62 study sites in 16 countries. The endpoints were assessed by the similar examinations as Protocol 015, but in addition had an evaluation of the genital lesions (HPV DNA sampling for HPV types 6, 11, 16, 18) for genital warts, VIN, VaIN, vulvar cancer and vaginal cancer. The vaccine, in the per-protocol population, had 100% efficacy (95% CI 78.5% -100%) against cervical cancer (CIN 2, 3 or AIS, related to HPV 6, 11, 16, or 18) and 100% efficacy (95% CI; 86.4% -100%) against genital warts (related to HPV 6, 11, 16 or 18). (1,13)

### COMBINED ANALYSIS

Data from the four clinical studies indicated protection against HPV-16 or 18 related to CIN 2/3 or AIS was 100% (CI: 92.9% to 100%). Combined data from three trials using the QHV (Protocols 007,013, 015) showed protection for CIN attributed to HPV 6,11, 16, 18; the efficacy rate was 95.2% (CI= 87.2% -98.7%). In the vaccine group, there were four cases of CIN but they were CIN 1. The vaccine was also efficacious against external genital lesions related to HPV 6, 11, 16, or 18 in 98.9% (CI: 93.7% - 100%) of the participants. The QHV was also shown to be efficacious against HPV 16 or 18 related VIN 2/3, or VaIN 2/3 in 100% (CI: 55.5 to 100) of the participants. (1,13)

### PATIENTS WITH PREVIOUS INFECTION

The clinical trials did not exclude patients if they were HPV DNA or antibody positive at entry, so additional data is available for this patient population. Less than 1/3 of the population had evidence of prior exposure to one of the vaccine HPV types. Of those participants that were positive for one or more HPV types, the vaccine had high efficacy for preven-

tion of the other HPV types. (1)

### **IMMUNE RESPONSE**

In all studies, greater than 99% of participants had an immune response to all HPV types 1 month after completing the three-dose series.

Vaccination seems to provide higher antibody titers than natural infection, but the minimal titer to confer protection is not known. The antibody titers have been detected up to 60 months and may be longer. Additional information on duration of immunity will be evaluated in future publications. (1)

### **SAFETY**

Local and systemic adverse reactions have been observed in clinical trials. Pain at the injection site was reported in 83.9% of the vaccine group, 75.4% in the aluminum adjuvant group and 48.6% in the placebo group. In addition, swelling and erythema were commonly reported. The local reactions were regarded as mild or moderate in the majority of the participants. (13)

Systemic adverse events among female participants aged 9 to 23 were most commonly reported as fever, nausea and nasopharyngitis in 13%, 6.7%, and 6.4%, respectively in the vaccine group. In the placebo group, the rate of adverse events was similar to the vaccine group. Majority of the adverse effects were mild to moderate in severity. (1,13)

Overall, vaccine-related severe adverse events occurred in <0.1% of persons. (1,13)

### **PREGNANCY/LACTATION**

The clinical trials excluded pregnant women from the study. Pregnancy tests were conducted prior to administration of the vaccine. If the participant was found to be pregnant, the vaccine was delayed until completion of pregnancy. Nevertheless, there were over 1,200 women in both the vaccine and placebo groups that were pregnant during the trials and the percentage of spontaneous loss was similar in both groups. (MMWR) The QHV is considered pregnancy category B based on animal data indicating no harm to the fetus. (13)

It is not known if the QHV is excreted in the breast milk. In the clinical trials, 995 participants (500 in the vaccine group and 495 in the placebo group) were breast-feeding during the vaccination period. Adverse events occurred in 3.4% of the vaccine and 1.8% of the placebo group in the lactating women, but none were determined to be vaccine related.

### **COST AND ECONOMIC IMPACT**

The retail cost of the vaccine is approximately \$150 per dose. (16) To alleviate the cost burden, the QHV has been added to the Federal Vaccines for Children Program which covers the cost for those individuals with financial hardship.

The economic burden of the prevention and treatment of HPV-related diseases, specifically anogenital warts and cervical HPV diseases is estimated at over \$4 billion dollars in direct costs in the United States each year. The cost would be more substantial, if this included vaginal and anal cancer and RRP.

Various models have been developed to evaluate the impact of the HPV vaccine suggesting that vaccinating an entire cohort of females aged 12 years of age could reduce their lifetime risk of cancer by 20% to 66%. (1) Cost-effectiveness models of routine HPV vaccinations in females aged 12 years old have indicated that cost per quality-adjusted life year (QALY) can range from \$3000 to \$24,300.

### **FDA APPROVED INDICATION / SUMMARY**

The quadrivalent Recombinant vaccine was approved by the FDA in 2006. See Table 3

Based on the above data, the Advisory Committee of Immunization Practices (ACIP) recommends the quadrivalent HPV vaccine be given routinely for females aged 11 to 12 years of age, but can be administered as early as 9 years of age. It is currently licensed for females aged 9 to 26 years of age. Vaccination of females who have not been vaccinated over the age of 12 and younger at 26 years of age can be given the series. Females that are not sexually active should benefit from the vaccination. Sexually active females may be infected with HPV, but not all 4 types in the vaccine. The clinical trials suggest that females will be protected from the HPV types that they are not infected with. (1,13)

Despite administration of the vaccine, cervical cancer screening in females has not changed and should occur routinely. Health care providers should educate women about the importance of routine cervical cancer screening. (1)

The groups in which the vaccine is not licensed for includes females <9 years of age and women > 26 years of age. Women greater than the age of 26 may benefit from the HPV vaccine, but the efficacy rates are not known; clinical studies are underway. (17)

The QHV is not licensed in men, but there is immunogenicity and safety data in males aged 9 to 15 years of age. (1,13) Efficacy studies are underway in males. HIV positive men who sleep with men are at higher risk for HPV infection; studies are in progress to determine the effectiveness in this specific population. In addition, more studies are ongoing in other immunosuppressed populations (lupus, Solid-organ transplant patients, etc); these individuals may be considered for vaccination because it is a noninfectious vaccine, but, the immune response may be less. (17)

**PRECAUTIONS AND CONTRAINDICATIONS**

Patients with moderate to severe illness should be deferred vaccination until the patient improves, but patients with minor acute illnesses can be given the vaccine. The QHV is contraindicated for patients with a history of immediate hypersensitivity to any vaccine component. Data from the Vaccine Adverse Event Reporting System (VAERS) indicates that the recombinant yeast used in the vaccine production is a minimal risk for anaphylactic reaction in patients with history of allergic reaction to *Saccharomyces cerevisiae* (baker's yeast). Syncope has occurred after the administration of the vaccine among adolescents and young adults, as indicated by the VAERS data. It is recommended that health care providers observe patients for 15 minutes after administration. (13)

**CONTROVERSIES**

Since the approval of this vaccination, many states have mandated HPV vaccines for school entrance. Opponents of mandatory vaccination include anti-vaccine activists who argue that the vaccine has not been sufficiently studied, and specific religious organizations who oppose mandatory vaccination on moral grounds.

The long term efficacy and safety have been questioned in this vaccine. As mentioned earlier, antibody titers have been detected up to 5 years, but it is unknown if the protection will still provide benefit up to the time of the development of cervical cancer which takes decades to develop. Also, it is unknown if a booster vaccination is needed. (18)

Over 16 million doses of the QHV have been administered to females and 10,000 adverse incidents have been reported to the FDA and CDC via the VAERS. Ninety-four percent of the cases are considered to be non-serious, which included fainting, headaches, nausea, fever, and pain and swelling at the injection site. The remaining adverse event reports included serious reactions such as cases of Guillain-Barré syndrome, blood clots, and deaths. The analysis of these reports did not suggest a pattern and therefore are not thought to be vaccine related. (19)

**BI-VALENT HPV VACCINE**

A bivalent vaccine (HPV 16 and 18) for the prevention of HPV-related cervical diseases is being studied. Similar to the quadrivalent vaccine, the bivalent vaccine is efficacious (> 90%) in preventing persistent infection against vaccine specific HPV types in those that are HPV negative at the time of vaccination. It is less effective in women who were tested positive for HPV at the time of vaccination. It is important to differentiate between the bivalent and the quadrivalent vaccines, whereas the bivalent vaccine does not confer protection against genital warts (caused by HPV 6 and 11). The bivalent vaccine is not licensed as of April 2009, but evaluation by the FDA is anticipated in the near future. (18)

**CONCLUSIONS**

HPV is the most common sexually transmitted disease in the United States. Infection with the high-risk types can lead to precancerous and cancerous lesions. The QHV can confer protection against specific HPV types (6,11, 16, and 18) which are responsible for the majority of cervical cancer and genital warts. Controversies still remain about long-term efficacy and routine administration of the QHV.

Table 1: HPV-associated Cancers

Cancer	% Attributable to oncogenic HPV	HPV type most commonly associated
Cervix	100%	70% attributable to HPV 16 and 18
Anus	90%	Majority HPV type 16
Vulva	40%	Majority HPV type 16
Vagina	40%	Majority HPV type 16
Penis	40%	Majority HPV type 16

Table 2: Guidelines for screening for cervical cancer in the United States

Guidelines	American Cancer Society	US Preventive Services Task Force
When to test	Approximately 3 years after onset of vaginal intercourse, but no later than 21 years of age	Within 3 years of onset of sexual activity or age of 21 years, whichever comes first
Frequency of conventional Pap test	Annually; every 2-3 years for women aged >30 years with three negative cytology tests	At least every 3 years
If HPV testing used as adjunct	Every 3 years if HPV negative, cytology negative	Insufficient evidence

Table 3: GARDASIL™ prescribing information

Indication	Dosage	Administration
GARDASIL™ is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types	IM administration as 0.5mL-dose at the following schedule: 0,2, 6 months	Shake Well GARDASIL® is a white, cloudy liquid. Do not mix with other vaccines Administer IM in the deltoid region of the upper arm or higher anterolateral area of the thigh.
	No drug interactions found with hormonal contraceptives	Syncope has been reported; observation is recommended after 15 minutes after vaccination
		Can be administered with RECOMBIVAX HB hepatitis B vaccine

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**REMAINING TOPICS FOR 2009**

<b>Herbals</b>	<b>Current Status of Hormone Replacement Therapy</b>
<b>Contemporary Parkinson's Therapy</b>	<b>Commonly Acquired MRSA</b>
<b>Update: Chronic Fatigue Syndrome &amp; Fibromyalgia</b>	<b>Review &amp; Update on Immunizations</b>

Fill in the information below, answer questions and return **Quiz Only** for certification of participation to:  
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CHECK IF NEW ADDRESS  **ARE YOU LICENSED IN FLORIDA? IF YES FL LIC** \_\_\_\_\_

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**LESSON EVALUATION**

Please fill out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

1. Does the program meet the learning objectives?

Discuss the epidemiology of HPV infection in the U.S. Yes No

Describe the natural history & clinical sequelae of HPV infection Yes No

List the treatment & prevention options for HPV infection Yes No

Comment upon the indications, efficacy & economic impact of the HPV vaccine Yes No

2. Was the program independent & non-commercial Yes No

	Poor			Average		Excellent	
	1	2	3	4	5	6	7

3. Relevance of topic

4. What did you like most about this lesson? \_\_\_\_\_

5. What did you like least about this lesson? \_\_\_\_\_

**Please Select the Most Correct Answer**

1. What percentage of cervical cancer is caused by HPV?  
 A. 58%  
 B. 100%  
 C. 90%  
 D. It is unknown

6. What is the administration schedule for the QHV?  
 A. 0, 2, 6 months  
 B. 0, 1, 3 months  
 C. 0, 1 months  
 D. 2, 6 months

2. Which is the most common mode of HPV transmission?  
 A. Fecal-oral route  
 B. Vertical transmission  
 C. Airborne  
 D. Genital contact

7. The bi-valent vaccine under investigation will not protect against?  
 A. Genital warts  
 B. HPV 6, 11  
 C. Cervical cancer  
 D. A and B

3. The quadrivalent HPV contains which of these HPV types?  
 A. HPV 6, 11  
 B. HPV 6, 11, 16, 18  
 C. HPV 16, 18  
 D. HPV 6, 11, 18, 52

8. When is the most efficacious time to vaccinate individuals?  
 A. Before sexual debut  
 B. After sexual encounter  
 C. After age 26  
 D. Before age 9

4. What is the common adverse reaction with the FDA approved HPV vaccine?  
 A. Injection site pain  
 B. Nausea  
 C. Swelling  
 D. Seizures

9. In the clinical trials, women who tested positive for specific HPV types before the administration of the vaccine were found to be protected against other HPV types found in the vaccine.  
 A. True      B. False

5. Which of the following groups is the vaccine not licensed for?  
 A. Less than 9 years of age  
 B. Age 11-12  
 C. Males  
 D. A & C

10. In the combined analysis of the QHV trials, the QHV was effective (>90%) in preventing:  
 A. CIN 2 or 3  
 B. Genital warts  
 C. VIN, VaIN  
 D. All of these

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