National PBM Drug Monograph

Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine (Gardasil®)

February 2007

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

Gardasil® is a quadrivalent recombinant vaccine which contains a mixture of four types of viral-DNA free virus like particles (VLP). These VLP are derived from the major capsid (L1) proteins of HPV types 6, 11, 16 and 18. Gardasil is not a live virus vaccine and does not contain the HPV virus.

Gardasil® is indicated for girls and women ages 9-26 for prevention of the following diseases caused by human papillomavirus (HPV) types, 6, 11, 16 and 18:

1. Cervical cancer
2. Genital warts (condyloma acuminate)

And the following precancerous or dysplastic lesions:

1. Cervical adenocarcinoma *in situ* (AIS)
2. Cervical intraepithelial neoplasia (CIN) grade 2 and 3
3. Vulvar intraepithelial neoplasia (VIN) grade 2 and 3
4. Vaginal intraepithelial neoplasia (VaIN) grade 2 and 3
5. Cervical intraepithelial neoplasia (CIN) grade 1

Efficacy:

Data from two published studies (n=552, n=241) and two unpublished studies (n=5445, n=12,167):

- The quadrivalent vaccine was 90% effective or greater in preventing infection and cervical or external genital disease associated with HPV types 6/11/16/18 in women who were naïve to HPV vaccine types.
- In the analysis which included all women regardless of baseline HPV status and who received at least one vaccination, the vaccine prevented cervical disease in 40-42% of patients and external genital disease 68%, but the numbers needed to treat were similar. (This analysis more closely resembles intent to treat analysis and a "real world" approach).
- At this time, the American College of Obstetricians and Gynecologists (ACOG) and the American Cancer Society (ACS) do not recommend testing for HPV prior to vaccination. They indicate that testing does not identify past HPV infection, only current infection. Serologic testing for HPV is considered unreliable and not commercially available. Finally, requiring HPV testing prior to vaccination would significantly increase the cost associated with vaccination
- The quadrivalent vaccine is not a therapeutic vaccine so it will not be effective in treating infection or disease associated with the vaccine HPV types in women who have been infected with one of the HPV vaccine types. However, it will be effective at preventing infection or disease associated with HPV vaccine types in which they have not been infected.
- In all four of the efficacy studies, the immunogenicity of the quadrivalent HPV vaccine was measured using various competitive immunoassays. Geometric mean titers (GMTs) were used to evaluate the subject's response to vaccine (immunogenicity) and to determine the duration of its

effectiveness. The challenge in testing the response to the vaccine is that the concentrations of anti-HPV vaccine-specific antibodies (6/11/16/18) needed to confer prevention against infection or from disease related to HPV vaccine types is not known. The anti-HPV 6/11/16/18 antibody response to the vaccine was nearly 100% and appeared to be greater in girls compared to adult women (1.7-2.7 fold greater). Anti-HPV geometric mean antibody titers remained above those observed in women with a prior natural history of HPV infection through 36 months. In a smaller group of patients, anti-HPV antibody GMTs remained at or above those in women with natural HPV infection through 60 months. At this time, the duration of the vaccine's effectiveness is not known. There is inadequate data to conclude if and when a booster vaccine may be indicated.

Dosage and Administration:

- Gardasil® is administered intramuscularly as 3 separate 0.5 ml doses. The first dose is followed by 2 additional doses given at 2 and 6 months after the initial dose.
- The vaccine should be shaken well immediately before use. No reconstitution or dilution is necessary. The vaccine should be given intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.
- The vaccine should be refrigerated (2-8ºC, 36-46ºF). It should be protected from light and should not be frozen.

Safety:

- The safety of the quadrivalent vaccine was evaluated in 21,464 patients in clinical trials with 0.1% withdrawing due to adverse events.
- Injection site ADEs were reported more often in the vaccine vs. placebo group. (90% rated as mild to moderate in intensity)
- Serious ADEs were reported in 102 subjects with headache, gastroenteritis and appendicitis most commonly reported.
- 9 of 11,813 (0.08%) subjects in the vaccine vs. 3 of 9,701 (0.03%) subjects in the placebo group developed arthritis (Juvenile or Rheumatoid) or systemic lupus erythematosus during follow up.
- Deaths during the trials were not unexpected and weren't considered related to the vaccine.
- Within 6 months of FDA approval (6-8-06), there were 82 reported adverse events associated with vaccination. Approximately one-quarter of those reports were neurologic in nature including syncope, seizures and Guillian-Barre Syndrome (n=3).
- Health officials are recommending a 15-minute waiting period after vaccination before leaving a physician's office.
- The quadrivalent vaccine is contraindicated in those with hypersensitivity to the active substances or excipients contained in the vaccine. Individuals with a history of immediate hypersensitivity to yeast should not receive the vaccine. Those who exhibit hypersensitivity after receiving a vaccination should not receive additional vaccinations with the quadrivalent product.
- In the case of a febrile illness, the decision to administer or delay the quadrivalent vaccine is dependent upon the severity and the etiology of the illness. Mild fever in the setting of an upper respiratory illness should not be considered a contraindication to vaccination.
- Individuals with an impaired immune response may have a reduced antibody response.
- Similar to other intramuscularly administered vaccines, the quadrivalent vaccine should not be given to individuals with bleeding disorders or to those patients treated with anticoagulants unless the benefit is believed to outweigh the risk of bleeding.
- Pregnant women should not receive the vaccine. If a woman becomes pregnant during the vaccination series, the remainder of the series should wait until after delivery.

Place in Therapy:

- Recommend following ACIP's recommendations regarding routine vaccination of girls aged 11 and 12 years and as early as age 9.
- Recommend catch up vaccination for those girls and women aged 13-18 years.
- Recommend OFFERING vaccination with the quadrivalent vaccine to those women 19-26 years of age.
- Reinforce the importance of continued routine screening for cervical cancer in both vaccinated and unvaccinated women.
- Do not recommend vaccination in women >26 years of age. Await evidence for the effective and safe use of the vaccine in this age group.
- Do not recommend vaccination in males.

Introduction

The American Cancer Society has estimated that in 2006, approximately 9,710 new cases of invasive cervical cancer will be diagnosed and 3,700 women will die from it.[1] The primary recognized cause of cervical cancer is persistent infection with human papillomavirus (HPV). Human papillomavirus is a common virus that can be passed between individuals through sexual contact. The Centers for Disease Control and Prevention (CDC) have estimated that each year, 6.2 million Americans become infected with HPV and that more than 50% of men and women have been infected with HPV at some point in their lives.[2] There are more than 100 HPV types with over 30 of them known to infect the anogenital tract. The various HPV types infecting the genital tract are sometimes referred to as "low risk" or "high risk" types. The low risk types rarely develop into cancer but persistent infection with the high risk types are more likely to lead to cancer. In the majority of cases, infection with HPV is benign and will resolve on its own. However, persistent infection with high risk HPV types is the most important predictor for cervical cancer development. There are approximately 15 HPV types that have been associated with the development of cervical cancer. Those types include the following and are listed in descending order of frequency of cervical cancer: 16, 18, 45, 31, 33, 52, 58, 35, 59, 56, 39, 51, 73, 68 and 66.[3] In general, the interval between acquiring infection with HPV and subsequent diagnosis of cervical cancer is 10 years or longer. Therefore cervical cancer is rare in women under 25 and is most often observed in women over 40.[4-5]

In June of 2006, the FDA approved the first vaccine indicated for the prevention of cervical cancer, abnormal and precancerous cervical lesions, abnormal or precancerous vaginal and vulvar lesions and genital warts. The vaccine is a quadrivalent recombinant vaccine effective against HPV types 16 and 18 which are responsible for approximately 70% of cervical cancer cases, and against HPV types 6 and 11 which cause about 90% of genital warts. HPV types 6 and 11 are also associated with the majority of cases of recurrent respiratory papillomatosis. In this monograph, the efficacy, immunogenicity, safety and applicability of this vaccine in the female veteran population will be discussed.

Pharmacology/Pharmacokinetics[6]

Gardasil® is a quadrivalent recombinant vaccine which contains a mixture of four types of viral-DNA free virus like particles (VLP). These VLP are derived from the major capsid (L1) proteins of HPV types 6, 11, 16 and 18. Gardasil is not a live virus vaccine and does not contain the HPV virus.

FDA Approved Indication(s) and Off-label Uses[6-7]

Gardasil® is indicated for girls and women ages 9-26 for prevention of the following diseases caused by human papillomavirus (HPV) types, 6, 11, 16 and 18:

- Cervical cancer

- Genital warts (condyloma acuminate)

And the following precancerous or dysplastic lesions:

- Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 2 and 3
- Vulvar intraepithelial neoplasia (VIN) grade 2 and 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and 3
- Cervical intraepithelial neoplasia (CIN) grade 1

***Cervical cancer screening recommendations have not changed**.

The **Advisory Committee for Immunization Practices (ACIP)** to the CDC has recommended routine use of this vaccine in girls 11-12 years of age and as early as age 9 (prior to sexual debut). Additionally, vaccination of girls and women ages 13-26 years. The ACIP also provided recommendations for special situations in which the vaccine can be given. Those situations include women with equivocal or abnormal Pap smear test, positive HPV test (Hybrid Capture II®) or genital warts. Women who are lactating can receive the vaccine. Finally, the vaccine can be administered to immunosuppressed women but the response may be less than in immunocompetent women.

There is interest in administering the quadrivalent HPV vaccine to women >26 years of age for similar indications. However, the American College of Obstetricians and Gynecologists (ACOG), the American Cancer Society (ACS) and the ACIP have been unable to provide guidance for administering this vaccine to women older than 26 years of age because of a lack of evidence in this age group. The FUTURE III trial expects to enroll 3800 women 24-45 years of age to determine the efficacy of the vaccine in reducing the incidence of infection and disease (genital warts, vulvar, vaginal and cervical cancer) associated with HPV types 6/11/16/18. Data from FUTURE III will help determine benefit in those >26 years of age. The quadrivalent HPV vaccine is not recommended in males at this time.

Table 1: Specialty Organization Recommendations for Administering HPV Vaccine [15-17]

Specialty Organization	Females 9-12 Years (Prior to Sexual Debut)	Females 13-18 Years	Females 19-26 Years	Females >26 Years	Men and Boys
ACIP	Recommended	Recommended	Recommended	Not addressed in provisional recommendations.	Do not recommend
ACOG	Recommended	Offer vaccine	Offer vaccine	Data insufficient to make recommendations.	Do not recommend
ACS	Recommended	Recommended	Insufficient data to recommend for or against*	Not currently recommended.	Do not recommend

*Limited efficacy data for women in this age group since most had an average of 2 and not more than 4 lifetime sexual partners, absence of data for women with >4 lifetime sexual partners, lack of cost-effectiveness data in this age group.

Current VA National Formulary Alternatives

There are no formulary or non formulary alternatives to Gardasil®

Dosage and Administration

Gardasil® is administered intramuscularly as 3 separate 0.5 ml doses. The first dose is followed by 2 additional doses given at 2 and 6 months after the initial dose.

The vaccine should be shaken well immediately before use. No reconstitution or dilution is necessary. The vaccine should be given intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

The vaccine should be refrigerated (2-8ºC, 36-46ºF). It should be protected from light and should not be frozen.

(Contents of vaccine: 20 mcg HPV 6 L1 protein/40 mcg HPV 11 L1 protein/40 mcg HPV 16 L1 protein/20 mcg HPV 18 L1 protein. Also 225 mg aluminum (as amorphous aluminum sulfate adjuvant), 9.56 mg NACL, 0.78 mg L-histidine, 50 mcg polysorbate 80, 35 mcg sodium borate and water for injection. The product does NOT contain preservatives).

Efficacy (For further details on the efficacy results of the clinical trials, refer to Appendix A-Clinical Trials)

Efficacy Measures

Investigators of the quadrivalent HPV vaccine met with FDA Officials to identify appropriate endpoints in designing clinical trials. It was determined that reduction in the incidence of vaccine type-specific persistent infection and reduction of associated cervical intraepithelial neoplasia (CIN1, CIN2 and CIN 3) and carcinomas *in situ* would serve as trial endpoints. Other endpoints included external genital lesions (e.g. condylomas, vulvar intraepithelial neoplasia (VIN), vaginal intraepithelial neoplasia (VaIN)). The use of cervical cancer as a primary clinical endpoint was considered unethical since cervical cancer screening can essentially prevent most cervical cancers (precancerous lesions are identified through routine screening and are most often treatable). Additionally, the trials were not of a sufficient duration to evaluate this endpoint. Investigators also tested the immunogenicity of the quadrivalent HPV vaccine to determine the anti-HPV antibody response and the duration of its effectiveness.

The trials included in this section are limited to those trials in which the efficacy, immunogenicity and safety of the quadrivalent vaccine are examined. There are a limited number of trials evaluating the efficacy of a single vaccine HPV type (monovalent). However, those trials will not be included in this monograph but are available elsewhere.[8]

Efficacy Findings

a. Prevention of Persistent Infection and Disease Related to HPV 6/11/1/6/18

To date, there have been two published [9,12] and two unpublished [10-11] completed trials evaluating the efficacy of the quadrivalent vaccine in preventing infection or disease related to HPV types 6/11/16/18 in approximately 18,164 women. In each trial, women between the ages of 15-26 were randomized to the quadrivalent vaccine or placebo vaccine to be administered at day 1 and months 2 and 6. Women were included if they were healthy, non-pregnant, no prior history of abnormal Pap tests and had a lifetime history of no more than 4 sexual partners. In both published studies, women with a prior history of HPV infection were not excluded. In each trial, efficacy analyses were conducted on more than one population. The per-protocol efficacy analysis (PPE) was the primary efficacy analysis. The modified intent to treat (MITT) analyses of which there is more than one were prespecified and intended to be supportive (See table 2).

Table 2: Definition of Populations Analyzed

Population Analyzed (Study using analysis)	Population Included
Per-Protocol Efficacy Analysis (PPE) *All 4 studies used this definition (efficacy analyzed beginning at 7th month) and was the primary efficacy analysis.	1. Subjects seronegative and PCR negative to HPV vaccine types (6/11/16/18) at day one and through month seven (through vaccination series). 2. Received all 3 vaccinations 3. No protocol violations.
Modified Intent to Treat (MITT)	1. Subjects seronegative and PCR negative to HPV vaccine types

*Published studies (efficacy analyzed beginning after day 30)	(6/11/1/6/18) at day 1. 2. Received at least 1 vaccination
Modified Intent to Treat (MITT-1) *FUTURE I	1. Subjects seronegative and PCR negative to HPV vaccine types (6/11/16/18) at day one and through month seven (through vaccination series). 2. Received all 3 vaccinations 3. Some protocol violations accepted
Modified Intent to Treat (MITT-2) *FUTURE I and FUTURE II+	1. Subjects seronegative and PCR negative to HPV vaccine types (6/11/1/6/18) at day 1. 2. Received at least 1 vaccination Restricted MITT-2 (Used in FUTURE I) 1 and 2 above but also with a normal Pap test (intended to mimic "real world" estimate of the impact of the vaccine on clinical disease in HPV naïve women.
Modified Intent to Treat (MITT-3) *FUTURE I and FUTURE II+	1. Initial HPV PCR and serology not relevant for inclusion 2. Received at least 1 vaccination
Modified Intent to Treat (MITT-4) *FUTURE I	1. Subjects seronegative and PCR negative to HPV Vaccine types at day 1 and through month 3. 2. Received at least 2 vaccinations

+In FUTURE II, women had to be HPV naïve to types 16/18 to be included in various analyses. HPV=human papillomavirus, PCR-polymerase chain reaction

The first trial was a phase II dose ranging study done in 2 parts. In the first part, just over 1100 women were randomized to 3 different doses of the vaccine vs. 2 different aluminum adjuvant placebo vaccines. The intent of this part of the study was to determine the immunogenicity (response to vaccine) at various doses and the efficacy. The anti-HPV antibody response was similar between all 3 active vaccines. As a result, the "low dose" vaccine was selected for development. In the second part of the study (n=552), those randomized to the "low dose" vaccine were compared to the pooled placebo vaccine groups to determine the vaccines efficacy in preventing persistent infection or disease related to the HPV vaccine types (composite primary endpoint) over a 36 month period. During follow-up using the PPE analysis, four patients in the vaccine group developed infection or disease vs. 36 patients in the placebo group (Observed efficacy 90%, 95% CI 71-97, p<0.0001, NNT 7.3). No patient in the quadrivalent vaccine group developed cervical or external genital disease associated with HPV vaccine types vs. 6 in the placebo group (Observed efficacy 100%, 95% CI 16-100, p=0.0151, NNT 38). Four patients in the vaccine group were identified as having persistent infection with HPV type 16 (n=3) or HPV type 18 (n=1) vs. 35 in the placebo group (HPV type-n, respectively: HPV 6-13, HPV 11-3, HPV 16-21, HPV 18-9) (Observed efficacy 89%, 95% CI 70-97, p<0.0001, NNT 7.5)). When analyzing the MITT population, the observed efficacy differences were similar.

The second published study was a 2 year extension trial in which those women in the "low dose" vaccine groups and placebo groups were invited to participate. Only women from Brazil and Nordic countries and not the US were invited. In the extension phase, the intent was to examine the efficacy and duration of immunogenicity over a period of 5 years (initial study 3 years plus 2 year extension). Two hundred and forty one women participated. For the PPE primary analysis, there were 2 cases of infection or disease in the vaccine vs. 46 cases in the placebo group (Observed efficacy 95.8%, 95% CI 83.8-99.5). No patients in the vaccine group developed disease vs. 6 in the placebo group (Observed efficacy 100%, 95% CI 12.4-100). Two patients developed persistent HPV infection in the vaccine (1-HPV 16 and 1-HPV 18) vs. 45 in the placebo group (Observed efficacy 95.6%, 955 CI 83.3-99.5). The MITT analysis demonstrated similar results. There were no new cases of infection in the vaccine group in the extension study.

The largest studies to date evaluating the quadrivalent vaccine are FUTURE I (n=5445) and FUTURE II (n=12,167). These studies are not yet published. As a result, data provided are taken from the manufacturer's summary of the data. (MITT-3 most resembles intent to treat and "real world" scenario)

Table 3: FUTURE I and FUTURE II

Trial	Primary Endpoint	PPE (observed efficacy %) NNT	MITT (observed efficacy %) NNT
FUTURE I (n=5445) 2.4 years	Disease related to HPV Types 6/11/16/18 (CIN or external genital disease)	**CIN 1-3**: Vaccine-0, placebo-37 (100%) NNT=62.5 **EGD**: Vaccine-0, placebo-40 (100%) NNT=57	**CIN 1-3:** MITT-1: Vaccine-0, placebo-39 (100%) NNT=62 MITT-2: Vaccine-2, placebo-57 (96.5%) NNT=50 MITT-3: Vaccine-65, placebo 113 (42.9%) NNT=55 MITT-4: Vaccine 1, placebo-53 (98.1%) NNT=48 **EGD:** MITT-1: Vaccine-0, placebo-43 (100%) NNT=59 MITT-2: Vaccine-3, placebo-59 (94.9%) NNT=50 MITT-3: Vaccine-26, placebo-80 (67.8%) NNT=50 MITT-4: Vaccinne-0, placebo-53 (100%) NNT=48
FUTURE II (n=12,167) 2 years	Disease related to HPV Types 16/18 (high-risk types, CIN 2/3 and AIS	**CIN 2/3, AIS or worse:** Vaccine-0, placebo-21 (100%) NNT=250	**CIN 2/3, AIS or worse:** MITT-2: Vaccine-1, placebo-66 (97.2%) NNT=100 MITT-3: Vaccine-68, placebo-116 (40.9%) NNT=125

*AIS=adenocarcinoma in situ, CIN-cervical intraepithelial neoplasia, EGD=external genital disease (vulvar, vaginal intraepithelial neoplasia or warts), MITT-modified intent to treat analysis (definitions are in table 2 on page 5), PPE=per-protocol efficacy analysis

Data Presented to the FDA[21]

From the available data supplied by the manufacturer, a combined analysis of trials was prepared and presented to the FDA. In the combined analysis, HPV 16/18 related CIN 2/3 or worse was determined in the PPE and MITT-3 populations. The results of the combined analysis were similar to what was observed in FUTURE II (PPE analysis: efficacy 100% [0 cases vaccine, 53 placebo, NNT 166)]; MITT-3 analysis: 39% efficacy [122 cases vaccine, 201 placebo, NNT 125]).

When the analysis was performed by HPV type in the MITT-3 population, the vaccine was 73.7% effective against CIN related by HPV 6/11, 45.6% effective against CIN related to HPV 16 and 69.7% effective against CIN related to HPV 18.

When examining the MITT-3 population from a pooled analysis of the clinical trials, the quadrivalent vaccine was only 12.2% effective against CIN 2/3 or worse caused by any HPV type.

When examining efficacy against HPV 6/11/16/18 related CIN 2/3 or worse and AIS, a higher number of cases were identified in the subgroup of patients found to be seropositive and PCR positive to the relevant HPV type associated with their disease (79 vaccine vs. 69 placebo, -25.8% effective). However, the total number of cases was higher (non-naïve subgroup) in the placebo group (121 vaccine vs. 130 placebo).

b. Immunogenicity

In all four of the efficacy studies [9-12], the immunogenicity of the quadrivalent HPV vaccine was measured using various competitive immunoassays. Geometric mean titers (GMTs) were used to evaluate the subject's response to vaccine (immunogenicity) and to determine the duration of its effectiveness. The challenge in testing the response to the vaccine is that the concentrations of anti-HPV vaccine-specific antibodies (6/11/16/18) needed to confer prevention against infection or from disease related to HPV vaccine types is not known. From the dose-ranging study, authors stated that the anti-HPV antibody response to types 6/11/16/18 was similar between all 3 doses of the vaccine. As a result, the lowest dose of

the vaccine tested was chosen for development. All vaccinated women demonstrated a response to vaccination as measured by geometric mean titers of anti-HPV 6/11/16/18 antibodies. Geometric mean titers in vaccinated women were greater than that of women in the placebo group with a previous history of natural infection (and cleared infection) with one of the HPV vaccine types. In the two smaller studies [9,12], vaccinated GMTs remained higher than those in women with natural infection, through 36 months and at or above those levels at 60 months. In the two year extension study [12] (total of 60 months), the difference for anti-HPV 18 antibody levels did not appear to be statistically different between vaccinated and those with prior natural exposure to HPV 18. Although anti-HPV antibodies in vaccinated women remained at or above levels observed in women with a prior natural infection to HPV (on placebo), the numbers of women in this group is very small to firmly conclude continued effectiveness of the vaccine against all 4 HPV types through 5 years.

Table 4: Antibody Response to Vaccination

	% Seropositive for anti-HPV 6/11/1/6/18 antibodies, respectively			
	Villa [9,13] (n=552)	Villa [12] (n=241) (extension study)	FUTURE I [10] (n=5445)	FUTURE II [11] (n=12,167)
Month 7	100% to 6/11/16/18	--	>99% 6/11/16/18	NR
Month 12	--	--	>99% 6/11/16 89% anti-HPV 18	NR
Month 18	98%/98%/100%/86%	--		NR
Month 24	--	--	>95% 6/11/16 73.6% anti-HPV 18	NR
Month 36	94%/96%/100%/76%	--	--	--
Month 60	--	GMTs in vaccinated women remained at or above the GMTs observed in the placebo treated women with a prior history of natural infection with HPV.	--	--

NR=not reported *Numbers of patients with in the 2-year extension study was small.

Summary of efficacy findings

From the available evidence, the quadrivalent vaccine was 90% effective or greater in preventing infection and cervical or external genital disease associated with HPV types 6/11/16/18 in women who were naïve to HPV vaccine types. In the analysis which included all women regardless of baseline HPV status and who received at least one vaccination (MITT-3), the vaccine was less effectiveness in preventing cervical disease (40-42%) and external genital disease (67.8%). At this time, the American College of Obstetricians and Gynecologists (ACOG) and the American Cancer Society (ACS) do not recommend testing for HPV prior to vaccination. They indicate that testing does not identify past HPV infection, only current infection. Serologic testing for HPV is considered unreliable and not commercially available. Finally, requiring HPV testing prior to vaccination would significantly increase the cost associated with vaccination.

The quadrivalent vaccine is not a therapeutic vaccine so it will not be effective in treating infection or disease associated with the vaccine HPV types in women who have already been infected with one of the HPV vaccine types. However, it will be effective at preventing infection or disease associated with HPV vaccine types in which they have not been infected.

The anti-HPV 6/11/16/18 antibody response to the vaccine was nearly 100% and appeared to be greater in girls compared to adult women (1.7-2.7 fold greater).[14] Anti-HPV geometric mean antibody titers remained above those observed in women with a prior natural history of HPV infection through 36 months. In a smaller group of patients, anti-HPV antibody GMTs remained at or above those in women with natural

HPV infection through 60 months. At this time, the duration of the vaccine's effectiveness is unknown. There is inadequate data to conclude if and when a booster vaccine may be indicated.

Adverse Events (Safety Data)[6]

Clinical trials of the quadrivalent HPV vaccine have enrolled more than 22,000 male and female participants with an average follow up period of two years in phase III trials and five years in phase II trials. The vaccine was well tolerated in the 21,464 patients examined for safety and tolerability with only 0.1% of individuals withdrawing due to an adverse experience. Injection-site events were reported more frequently with the vaccine than with placebo but more than 90% of subjects rated their injection site adverse experience to be mild or moderate in intensity. Serious adverse events were reported by 102 of the 21,464 subjects with headache, gastroenteritis and appendicitis being reported most commonly. Deaths reported during the clinical trial follow up period were consistent with fatal events occurring in healthy adolescents and adults, were not unexpected and weren't felt to be related to the vaccine (see tables below). Finally, 9 of 11,813 (0.08%) vaccine and 3 of 9,701 (0.03%) placebo recipients developed a new diagnosis of arthritis (Juvenile or Rheumatoid) or systemic lupus erythematosus during follow up.

Table 5: Vaccine-Related Injection-Site Reports of Adverse Effects[6]

Adverse Experience (Injection Site 1-5 days post vaccination)	Quadrivalent HPV Vaccine (N=5088) %	Aluminum-Containing Placebo (N=3470) %	Saline Placebo (N=320) %
Pain	83.9	75.4	48.6
Swelling	25.4	15.8	7.3
Erythema	24.6	18.4	12.1
Pruritis	3.1	2.8	0.6

*Table adapted from Gardasil® Product Information

More than 90% of vaccine recipients considered their adverse injection-site experience with the quadrivalent HPV vaccine to be mild to moderate in intensity.

Table 6: Common Systemic Adverse Effects[6] (reported in 1% or more)

Adverse Experience (1-15 days post vaccination)	Quadrivalent HPV Vaccine (N=5088) %	Placebo (N=3790) %
Pyrexia (fever)	13	11.2
Nausea	6.7	6.6
Nasopharyngitis	6.4	6.4
Dizziness	4	3.7
Diarrhea	3.6	3.5
Vomiting	2.4	1.9
Myalgia	2	2
Cough	2	1.5
Toothache	1.5	1.4
Upper Respiratory Tract Infection	1.5	1.5
Malaise	1.4	1.2
Arthralgia	1.2	0.9
Insomnia	1.2	0.9
Nasal Congestion	1.1	0.9

*Table adapted from Gardasil® Product Information

Table 7: Most Commonly Reported Serious Adverse Events[6]

Adverse Experience (1-15 days post any vaccination)	Quadrivalent HPV Vaccine %	Placebo %
Headache	0.03	0.02
Gastroenteritis	0.03	0.01
Appendicitis	0.02	0.01
Pelvic Inflammatory Disease	0.02	0.01

*There were 102 serious adverse events reported in 21, 464 males and females enrolled in clinical trials of Gardasil®.

Table 8: Deaths Reported During Clinical Trials[6]

Cause of Death	Quadrivalent HPV Vaccine (#)	Placebo (#)
Motor Vehicle Accident	4	3
Overdose/Suicide	1	2
PE/DVT	1	1
Other	2-sepsis, 1-pancreatic cancer, 1-arrhythmia	1-asphyxia

*There were 17 deaths reported in the 21,464 males and females participating in clinical trials of Gardasil®. The deaths were considered to be consistent with fatal events occurring in healthy adolescents and adults and were not unexpected.

There were an equal number of congenital anomalies reported during the trials (15 vaccine vs. 16 placebo). However, there was an imbalance in the number of anomalies in women who reported conception within 5 days of vaccination (5 vaccine vs. 0 placebo). No pattern existed. The FDA has recommended a pregnancy register to further examine the safety of the quadrivalent vaccine in pregnancy. [21]

Post-Marketing Safety [18]

The National Vaccine Information Center www.NVIC.org recently prepared a report based upon information obtained from the federal Vaccine Adverse Event Reporting System (VAERS). In that report, they identified 82 reports of ADEs from the quadrivalent vaccine in 84 young girls and 2 boys (age range 11-27) within 6 months of FDA approval (approval 6-8-06). Sixty-three percent of the ADEs occurred on the day of vaccination and all except 3 were reported within one week. One-quarter of all reports involved neurologic ADEs including loss of conscientiousness, syncope and syncopal events and seizures. Another 5 cases involved dizziness and faintness. From the reports, one cannot be determined whether the 22 girls who experienced syncope may have experienced atonic seizures. Four girls were observed having seizure-like activity. Although the details of the events following vaccine-related ADEs are not known for many of the reported cases, there are several cases in which the event resulted in injury. Guillain-Barre Syndrome (GBS) was reported in two individuals who received the vaccine.

As of February 2007, there has been an estimated 542 reported ADEs associated with Gardasil administration including injection site soreness (20%), faintness or dizziness (11%) and nausea and fever (9%). At this time, health officials from the CDC are recommending a 15 minute waiting period after vaccination prior to leaving a physician's office.

There are two phase IV studies that are planned. The first one is an observational safety study conducted in the U.S. to investigate serious ADE occurring within 60 days of vaccination. The second is the Nordic Long-Term Follow-up Study intended to follow patients enrolled in the FUTURE II. In this study, HPV related diseases will be examined as well as long term effectiveness and duration of immune response of the quadrivalent vaccine, potential safety signals and pregnancy outcomes.[21]

Precautions/Contraindications[6]

Precautions

In the case of a febrile illness, the decision to administer or delay the quadrivalent vaccine is dependent upon the severity and the etiology of the illness. Mild fever in the setting of an upper respiratory illness should not be considered a contraindication to vaccination.

Individuals with an impaired immune response may have a reduced antibody response.

Similar to other intramuscularly administered vaccines, the quadrivalent vaccine should not be given to individuals with bleeding disorders or to those patients treated with anticoagulants unless the benefit is believed to outweigh the risk of bleeding.

Pregnant women should not receive the vaccine. If a woman becomes pregnant during the vaccination series, the remainder of the series should wait until after delivery.

Contraindications

The quadrivalent vaccine is contraindicated in those with hypersensitivity to the active substances or excipients contained in the vaccine. Individuals with a history of immediate hypersensitivity to yeast should not receive the vaccine. Those who exhibit hypersensitivity after receiving a vaccination should not receive additional vaccinations with the quadrivalent product.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name: **quadrivalent HPV vaccine, human papillomavirus vaccine, HPV vaccine**

Quadramet (EDTMP): unlikely, severe

Growth hormone (Humatrope): unlikely, moderate

Hyaluronidase Recombinant: unlikely, moderate

HP Acthar Gel (ACTH): unlikely, moderate

Hepatitis B vaccine: possible, mild

LA/SA for trade name **Gardasil**:

Lamisil: unlikely, mild

Adacel (Tdap vaccine): possible, mild

Dermasil: possible, mild

Gelusil: possible, mild

Vistaril (hydroxyzine): possible, mild

Lioresal (baclofen): possible, moderate

Gammagard (IGIV): unlikely, moderate to severe

Drug Interactions[6]

The quadrivalent vaccine can be administered concomitantly with the hepatitis B vaccine. Co administration with other vaccines is not known.

In their provisional recommendations, ACIP indicates that the quadrivalent vaccine can be administered at the same visit as other age appropriate vaccinations including, tetanus-diphtheria-pertussis, tetanus-diphtheria and the tetravalent meningococcal conjugated vaccine (MCV4). However, there are no published data to support safely giving these vaccines concomitantly with the HPV vaccine.

Acquisition Costs

The quadrivalent vaccine is administered as a series of 3 vaccinations over a period of 6 months.

Table 9: Estimated Cost Impact of Treating Women Veterans Ages 9-26 Years

Drug	Per Dose	Cost/Series/Patient ($)	Cost to Treat All Female Veterans 9-26 years ($)
Quadrivalent Vaccine	$84.00	$252.00	$8,702,568.00

*Estimated cost of treating women 27-45 years (n=139,331) =$35,111,412; **18-26 (n=32,429) =$8,172,108**

VA Female patients by age for FY06 (Oct 05 to Sept 06)

FY06

Age	Unique Patients
9	100
10	83
11	96
12	82
13	135
14	269
15	316
16	407
17	617
18	881
19	1,179
20	1,573
21	2,385
22	3,371
23	4,765
24	5,647
25	6,198
26	6,430
Total 9 to 26	34,534

Pharmacoeconomic Analysis

There is one cost-effectiveness analysis of administration of a bivalent vaccine (HPV types 16/18) in twelve year old girls. Administration of a HPV vaccine to 12 year old girls would result in a 61.8% reduction in cohort cervical cancer cases and have a cost-effectiveness ratio of $14,583 per quality adjusted life year (QALY). Inclusion of young males in a vaccination program would further reduce cervical cancer by 2.2% at an incremental cost-effectiveness ratio of 442,039/QALY.[19] inclusion of males was not considered cost-effective.

In a second study, [20] a Markov model was used to estimate the lifetime costs and life expectancy of a hypothetical cohort of women screened for cervical cancer beginning at age 12 and followed through age 85. Three strategies were compared including: vaccination only; conventional cytology screening; and vaccination followed by screening. Assumptions included that all subjects were vaccinated at age 12 with

all 3 doses of a theoretical bivalent HPV vaccine (HPV types 16/18). It was assumed that the vaccine's duration of effectiveness would last 10 years. The most cost-effective approach was vaccination followed by biennial screening starting at 24 years of age (44,889/QALY). However, vaccination and annual screening beginning at age 18 was associated with the greatest reduction in cancer incidence and mortality ($236,250/QALY) vs. vaccination combined with annual screening at age 22. Finally, the cost-effectiveness of vaccination plus delay of screening was very sensitive to vaccination age, duration of vaccine's effectiveness and the cost of vaccination. The authors concluded that determining the optimal age for vaccination is of the utmost importance and should be a research priority.

There are no cost-effectiveness studies considering vaccination of girls or women over the age of 12.

Conclusions

The quadrivalent vaccine is recommended in girls 9-12 years of age and girls and women ages 13-26 years. In clinical trials, the vaccine was 90% effective at reducing infection with HPV vaccine types and 100% effective in reducing cervical and external genital disease in women (ages 15-26 years) who were naïve to HPV vaccine types. However, in the analysis that included most women, regardless of their baseline HPV status, and who received one vaccination, the results were less impressive (Cervical disease reduced 40-42%, external genital disease reduced 67.8%) but the numbers needed to treat were similar. Immunogenicity of the vaccine was measured using a variety of immunoassays. However, the GMTs necessary to confer protection against infection from the HPV vaccine types is not known. In one small study, most women were seropositive for HPV vaccine types through 36 and 60 months. At this time, the vaccine's duration of effectiveness is not known. The effectiveness of the vaccine in preventing infection or disease (associated with HPV 6/11/16/18) in women older than 26 years or in those women having more than four lifetime sexual partners is also not known.

From clinical trials, the vaccine was well tolerated with 0.1% withdrawing due to adverse events. Serious ADEs were reported in 102 of 21,464 subjects with headache, gastroenteritis and appendicitis being most commonly reported. From post-marketing surveillance (VAERS), there are a number of reported ADEs occurring after administration of the vaccine. One-quarter of those reports are neurologic in nature.

Place in Therapy

1. Recommend following ACIP's recommendations regarding routine vaccination of girls aged 11 and 12 years and as early as age 9.
2. Recommend catch up vaccination for those girls and women aged 13-18 years.
3. Recommend OFFERING vaccination with the quadrivalent vaccine to those women 19-26 years of age.
4. Reinforce the importance of continued routine screening for cervical cancer in both vaccinated and unvaccinated women.
5. Do not recommend vaccination in women >26 years of age. Await evidence for the effective and safe use of the vaccine in this age group.
6. Do not recommend vaccination in males.

References:

1. http://www.cancer.org/downloads/STT/CAFF2006PWSecured.pdf (accessed 12-5-06)
2. http://www.cdc.gov/std/HPV/STDFact-HPV.htm (accessed 12-5-06)
3. Munoz N, Bosch FX, Castellsague X, et al. Against Which Human Papillomavirus Types Shall We Vaccinate and Screen? The International Perspective. Int J Cancer 2004;111:278-285.
4. Schiffman M, Kjaer SK. Natural History of Anogenital Human Papillomavirus Infection and Neoplasia. J Natl Cancer Inst Monogr, Chapter 2, 2003;31:14-19.
5. Lowy DR, Schiller JT. Prophylactic Human Papillomavirus Vaccines. J Clin Invest 2006;116:1167-1173

6. Gardasil Product Information 2006. Merck, Whitehouse Station, NJ 08889, USA.
7. http://www.cdc.gov/nip/ed/ciinc/hpv.htm (accessed 12-5-06)
8. Siddiqui MAA, Perry CM. Human Papillomavirus Quadrivalent (types 6, 11, 16, 18) Recombinant Vaccine (Gardasil®) Drugs 2006;66:1263-1271.
9. Villa LL, et al. Prophylactic Quadrivalent Human Papillomavirus (types 6, 11, 16 and 18) L1 Virus-Like Particle Vaccine in Young Women: A Randomized, Double-blind, Placebo-Controlled Multicentre Phase II Efficacy Trial. Lancet Oncol 2005;6:271-278.
10. Phase III, Protocol 013, FUTURE I Study (Females United to Unilaterally Reduce Endo/Ectocervical Disease) AMCP Dossier, Merck, November 2006.
11. Phase III, Protocol 015, FUTURE II Study. AMCP Dossier, Merck, November 2006.
12. Villa LL, Costa RLR, Petta CA, et al. High Sustained Efficacy of a Prophylactic Quadrivalent Human Papillomavirus types 6/11/16/18 L1 Virus-Like Particle Vaccine Through 5 Years of Follow-up. Br J Cancer 2006;95:159-1466.
13. Villa L, Ault KA, Giuliano AR, et al. Immunologic Response Following Administration of a Vaccine Targeting Human Papillomavirus Types 6,11,16 and 18. Vaccine 2006;24:5571-5583.
14. Block SL, Nolan T, Sattler C, et al. Comparison of The Immunogenicity and Reactogenicity of a Prophylactic Quadrivalent Human Papillomavirus (Types 6,11,16 and 18) L1 Virus-Like Particle Vaccine in Male and Female Adolescents and Young Adult Women. Pediatrics 2006;118:2135-2145.
15. http://www.cdc.gov/Nip/recs/provisional_recs/hpv.pdf (accessed 2-13-07)
16. http://www.acog.org/departments/dept_notice.cfm?recno=7&bulletin=3945 (accessed 2-13-07)
17. http://caonline.amcancersoc.org/cgi/reprint/57/1/7 (accessed 2-13-07)
18. http://www.nvic.org/Diseases/HPV/HPVrpt.htm (accessed 2-13-07)
19. Taira AV, Neukermans CP, Sanders CD. Evaluating Human Papillomavirus Vaccination Programs. Emerging Infectious Diseases 2004;10:1915-1923
20. Kulasingam SL, Myers ER. Potential Health and Economic Impact of Adding A Human Papillomavirus Vaccine to Screening Programs. JAMA 2003;290:781-789.
21. http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4222S-2_files/frame.htm#slide0116.htm (accessed 2-26-07)

Contact person: Cathy Kelley, Pharm.D. VACO PBM/ cathy.kelley@va.gov

Appendix: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to January 2007t) using the search terms quadrivalent HPV vaccine, HPV vaccine and Gardasil. The search was limited to studies performed in humans and published in English. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. Currently, few of the clinical trials examining the efficacy and safety of the quadrivalent vaccine have been published. As a result, the manufacturer's product information and AMCP dossiers were used in addition to the published trials to summarize the randomized trials.

Clinical endpoints in the following trials include infection with HPV vaccine types (6, 11, 16, and 18) and cervical or external genital disease (e.g. cervical intraepithelial neoplasia or CIN 1, 2, 3, cervical cancer, external genital lesions caused by HPV types in the vaccine). Immunogenicity was measured at specified time points during the trial to determine immune response and duration of vaccine effectiveness.

Randomized Clinical Trials Involving Quadrivalent HPV Vaccine

<table>
<tr><th>Study</th><th>Population</th><th>Intervention/Outcome Measures</th><th>Results</th><th>Adverse Events/Comments</th></tr>
<tr>
<td>Villa 2005 [9]
Phase II, R, MC, DB, PC, dose-ranging
N=552 (277 vaccine, 275 placebo)
36 months</td>
<td>Two sub studies: The first involved 1158 women and compared 3 different doses of HPV vaccine components vs. placebo for safety. In the second study (n=552), the dose chosen for development (low-dose) was evaluated for efficacy in preventing persistent infection and disease and safety. Immuno-gemicity was also examined.
1) Inclusion criteria: healthy non pregnant women 16-23 years</td>
<td>Vaccine or placebo was given at baseline, at 2 months and at 6 months.
<u>Examinations to measure efficacy:</u>
a) GYN exams and Pap tests were done at baseline and months 7, 12, 24 and 36.
b) Cervical swabs for PCR analysis of HPV were done at baseline and months 7, 12, 18, 24, 30 and 36.
c) Blinded pathology panel and central lab read histology slides.
were determined by a panel of pathologists and central lab.
<u>Composite primary endpoint:</u> persistent infection with vaccine</td>
<td>Efficacy analysis conducted on 2 populations
Per-Protocol Efficacy (PPE) Analysis (Primary Efficacy Analysis)-included only women seronegative to and PCR negative to HPV vaccine types at baseline and through completion of vaccination series, received all 3 doses of the vaccine and did not violate the protocol-(Included 78% HPV 6/11, 73% HPV 16, 82% HPV 18). Efficacy period began from month 7.
Modified Intent to Treat Analysis-included subjects' naïve to HPV vaccine types at day 1 (seronegative and PCR negative) and had at least one vaccination. Efficacy counted from day 30.
<u>I. Per-Protocol Efficacy Analysis (PPE) (Primary Efficacy Analysis)-Infection or Disease related to HPV types 6/11/16/18</u>
<table>
<tr><th></th><th colspan="3">Vaccine (n=276)</th><th colspan="4">Placebo (n=275)</th></tr>
<tr><th></th><th>N</th><th>Cases</th><th>Incidence/100 pt-yrs at risk</th><th>N</th><th>Cases</th><th>Incidence/100 pt-yrs at risk</th><th>Efficacy Difference</th><th>95% CI (p) NNT</th></tr>
<tr><td>Primary Endpoint (infection or disease)</td><td>235</td><td>4</td><td>0.7</td><td>233</td><td>36</td><td>6.7</td><td>90%</td><td>71-97 (p<0.0001) NNT 7.3</td></tr>
<tr><td>Infection</td><td>235</td><td>4</td><td>0.7</td><td>233</td><td>35</td><td>6.5</td><td>89%</td><td>70-97 (p<0.0001) NNT 7.5</td></tr>
<tr><td>Disease</td><td>235</td><td>0</td><td>0</td><td>233</td><td>6</td><td>1.1</td><td>100%</td><td>16-100 (p=0.0151)</td></tr>
</table>
</td>
<td>Pain at the injection site and headache were the most commonly reported adverse events. There were no serious vaccine-related ADEs.
Power calculations estimated that 250 women were needed for each the vaccine and the placebo group to declare vaccine effective with a two sided alpha of 0.05. The PPE analysis excluded approximately 25% of patients due to seropositivity to one vaccine HPV type at baseline or during the vaccination period. The</td>
</tr>
</table>

with no prior abnl Pap smears, and 4 or < lifetime sexual partners. Those with prior HPV infection were not excluded. (Women from Brazil, Nordic countries and USA were enrolled)

type HPV 6/11/16/18 (2 or more visits), or cervical or external genital disease (CIN; VIN; VaIN; external genital warts; or cervical, vulval or vaginal cancer with HPV vaccine type DNA from tissue or from a swab of the lesion)

Immunogenicity
Response to vaccination, using geometric mean titers (GMT) of antibodies to vaccine type HPV, was measured.

								NNT 38
External Genital Lesions	235	0	0	233	3	0.5	NA	NA
CIN 1-3	235	0	0	233	3	0.5	NA	NA
HPV 6 related	214	0	0	209	13	2.6	100%	68-100 (p<0.0001)
HPV 11 related	214	0	0	209	3	0.6	NA	NA
HPV 16 related	199	3	0.6	198	21	4.5	86%	54-97 (p<0.0001)
HPV 18 related	224	1	0.2	224	9	1.7	89%	21-100 (p=0.0103)

*NA=number of events too small for meaningful comparison

**There were no infection or disease associated with HPV vaccine types 6/11 in the vaccine group vs. 13 placebo cases, 3 cases of persistent infection and no disease associated with HPV 16 vs. 21 events in placebo group and 1 persistent infection with HPV 18 in the vaccine group vs. 9 events in placebo.

II. Modified Intent to Treat Analysis (MITT) Infection or Disease related to HPV types 6/11/16/18

	Vaccine (n=277)			Placebo (n=275)				
	N	Cases	Incidence/100 pt-yrs at risk	N	Cases	Incidence/100 pt-yrs at risk	Efficacy Difference	95% CI (p) NNT
Primary Endpoint (infection or disease)	266	6	0.8	263	48	7.2	89%	73-96 (p<0.0001) NNT 6.25
Infection	256	6	0.8	254	47	7.1	88%	72-96 (p<0.0001) NNT 6
Disease	266	0	0	263	10	1.4	100%	56-100 (p=0.0009) NNT 26

MITT analysis did include most patients and the results were similar to the PPE analysis.

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>
<table>
<tr><td>External Genital Lesion</td><td>265</td><td>0</td><td>0</td><td>261</td><td>4</td><td>0.6</td><td>NA</td><td>NA</td></tr>
<tr><td>CIN 1-3</td><td>258</td><td>0</td><td>0</td><td>256</td><td>7</td><td>1.0</td><td>100%</td><td>32-100 (p=0.0072) NNT 37</td></tr>
</table>
*NA=number of events too small for meaningful comparison

<u>III. Immunogenicity</u>

The concentration of anti-HPV type-specific antibodies needed to confer protection against infection with HPV vaccine types is not known. However, all vaccinated women demonstrated a response to vaccination as measured by geometric mean titers (GMT) of antibodies. Vaccinated women GMT of anti-HPV type-specific antibodies were greater than that of women in the placebo group with a previous history of natural infection with one of the HPV vaccine types. Vaccinated women GMTs remained higher than those women with natural infection, throughout the 36 month study. At 36 months, 94-96% of women were seropositive for HPV 6/11, 100% for HPV 16 and only 76% for HPV 18.
</td>
<td></td>
</tr>
<tr>
<td>Phase III, Protocol 013, FUTURE I Study R, DB, MC, PC (data on file) [10]

N=5,445

2.4 years</td>
<td>Women 16-23 years and up to 4 lifetime sexual partners.

N= 2717 vaccine

N=2725 placebo</td>
<td>Quadrivalent HPV vaccine or placebo at day 1, month 2 and month 6.

<u>Examinations to measure efficacy</u>:

a) GU specimens (endo/ ectocervical, perianal and labial, vulvar and perineal) day 1 and months 3, 7 and every 6 months.

b) Pap testing regular intervals, abnl referred for colposcopy

c) Biopsies for HPV-related diagnoses and HPV typed

d) Blinded pathology panel and central lab</td>
<td>Five populations were analyzed for HPV type-specific efficacy analyses:

I. Per-protocol efficacy (PPE)-subjects received all 3 vaccinations, seronegative to HPV vaccine types at day one and PCR negative day 1 through month 7, no deviation from protocol. *The PPE analysis was the primary efficacy analysis.

II. Modified Intent to Treat-1 (MITT-1)-similar to PPE but with some protocol violations.

III. Modified Intent to Treat-2 (MITT-2)-subjects received at least one vaccination and were seronegative and PCR negative to vaccine HPV types on day 1. Restricted MITT-2-included all subjects who were seronegative and PCR negative to all vaccine HPV types with a normal Pap test on day 1 (Intended to represent “real world” estimate of the impact of the vaccine on clinical disease caused by HPV among baseline HPV-naïve women).

IV. Modified Intent to Treat-3 (MITT-3)-subjects receiving at least one vaccination and regardless of initial serology and PCR status.

V. Modified Intent to Treat-4 (MITT-4)-subjects who received at least 2 vaccinations and seronegative to vaccine HPV types on day 1 and PCR negative on day 1 through month 3.</td>
<td>Adverse events were pooled and are reported in the ADE section of this monograph.

MITT-3 is the closest representation of an intention to treat analysis since it includes all subjects regardless of whether they received all 3 vaccinations or had evidence of prior infection with HPV.</td>
</tr>
</table>

read histology slides.

Primary Endpoint: Prevention of HPV 6/11/16/18 related CIN 1-3 or external genital lesions (condyloma, VIN 1-3, VaIN 1-3, vulvar and vaginal cancer).

Immunogenicity was measured.

I. PPE Analysis: (through 1.5 years of follow up)

HPV 6/11/16/18 related CIN 1-3:

	N	Events (n)	Person-years at risk	Incidence/100 pt-yrs at risk
Vaccine (n=2717)	2240	0	3779.8	0 NNT 62.5
Placebo (n=2725)	2258	37	3787.4	1

*Observed vaccine efficacy=100%, 97.5% CI 87.4-100, p<0.001, NNT 62.5

HPV 6/11/16/18 related External Genital Lesions:

	N	Events (n)	Person-years at risk	Incidence/100 pt-yrs at risk
Vaccine (n=2717)	2261	0	3865.2	0 NNT 57
Placebo (n=2725)	2279	40	3868.4	1

*Observed vaccine efficacy=100%, 97.5% CI 88.4-100), p<0.001 NNT 57

MITT Analysis:

HPV 6/11/16/18 related CIN 1-3:

	Vaccine (n=2717)			Placebo (n=2725)				
	N	Cases	Incidence/100 pt-yrs at risk	N	Cases	Incidence/100 pt-yrs at risk	Observed efficacy	95% CI
MITT-1	2416	0	0	2422	39	1	100% NNT 62	90.1-100
MITT-2	2557	2	0	2573	57	1	96.5% NNT 50	86.7-99.6
MITT-3	2607	65	1.2	2611	113	2	42.9% NNT 55	21.9-58.6
MITT-4	2490	1	0	2490	53	1.1	98.1% NNT 48	89.1-100

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>
<u>HPV 6/11/16/18 related External Genital Lesions</u>:
Vaccine (n=2717) Placebo (n=2725)
<table>
<tr><th></th><th>N</th><th>Cases</th><th>Incidence/100 pt-yrs at risk</th><th>N</th><th>Cases</th><th>Incidence/100 pt-yrs at risk</th><th>Observed efficacy</th><th>95% CI</th></tr>
<tr><td>MITT-1</td><td>2439</td><td>0</td><td>0</td><td>2444</td><td>43</td><td>1</td><td>100%
NNT 59</td><td>91.1-100</td></tr>
<tr><td>MITT-2</td><td>2620</td><td>3</td><td>0.1</td><td>2628</td><td>59</td><td>1.1</td><td>94.9%
NNT 50</td><td>84.4-99</td></tr>
<tr><td>MITT-3</td><td>2671</td><td>26</td><td>0.5</td><td>2668</td><td>80</td><td>1.4</td><td>67.8%
NNT 50</td><td>49.3-80.1</td></tr>
<tr><td>MITT-4</td><td>2516</td><td>0</td><td>0</td><td>2511</td><td>53</td><td>1.1</td><td>100%
NNT 48</td><td>92.8-100</td></tr>
</table>
<u>Immunogenicity</u>
At month 7, >99% of vaccinated subjects were seropositive for all of the vaccine HPV types. At month 12, >99% were seropositive for HPV 6/11/16 but only 89% for HPV 18. At 24 months, >95% were seropositive for HPV 6/11/16, but only 73.6% were seropositive for HPV 18. In the placebo group, <5% of subjects were seropositive for any vaccine HPV type throughout the study.
</td>
<td></td>
</tr>
<tr>
<td>Phase III, Protocol 015, FUTURE II Study. R, DB, MC, PC (data on file) [11]

N=12,167

2 years</td>
<td>Women 15-26 years of age with no more than 4 lifetime sexual partners.</td>
<td>Quadrivalent vaccine or placebo on day 1 and at months 2 and 6.

<u>Examinations to assess efficacy:</u>

a) GU specimens (endo/ ectocervical, perianal and labial, vulvar and perineal) on day 1, month 7 and every 6 months.

b) Pap testing at regular intervals.</td>
<td>There were 3 different populations analyzed in this study.

I. Per-Protocol Efficacy (PPE) analysis (Primary efficacy analysis population)-subjects who received all 3 vaccinations, seronegative and PCR negative to HPV types 16/18 on day 1 through month 7 and generally did not deviate from the protocol

II. Modified Intent to Treat (MITT-2) analysis-subjects included who received at least one vaccination and were seronegative and PCR negative to the HPV types 16/18 on day 1.

III. Modified Intent to Treat (MITT-3) analysis-subjects included who received at least one vaccination regardless of initial serology and PCR status.

<u>I. PPE Analysis: HPV 16/18 related CIN 2/3 or AIS</u>
<table>
<tr><th></th><th>N</th><th>Cases (n)</th><th>% Efficacy</th></tr>
<tr><td>Vaccine (n=6082)</td><td>5301</td><td>0</td><td>100% (95% CI 80.9-100)</td></tr>
</table>
</td>
<td>Adverse events from this trial will be included in the safety section of this monograph</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td>c) Sera at scheduled visits.

d) Abnl Pap tests referred for colposcopy

e) Biopsies were obtained for HPV-related diagnoses and were HPV typed.

f) Histology slides were interpreted by a blinded pathology panel and central lab.

g) Vaccination report card was completed after each vaccination.

<u>Primary Outcome Measures:</u>

a) Incidence of composite endpoint of HPV types 16 and 18 related high-grade cervical abnormalities (CIN2/3) or HPV 16/18 related adenocarcinoma in situ (AIS) in subjects who are seronegative and PCR negative for HPV 16/18 at baseline through month 7.

b) Demonstrate vaccine is well-tolerated.

Immunogenicity was also measured.</td>
<td>
<table>
<tr><td></td><td></td><td></td><td>NNT 250</td></tr>
<tr><td>Placebo (n=6075)</td><td>5258</td><td>21</td><td>--</td></tr>
</table>
*p<0.001, NNT 250

<u>II. MITT-2 Analysis: HPV 16/18 related CIN 2/3, AIS or worse</u>
<table>
<tr><th></th><th>N</th><th>Cases (n)</th><th>Patient Years at risk</th><th>Incidence/100 pt-yrs at risk</th><th>Observed Efficacy (95% CI)</th></tr>
<tr><td>Vaccine (n=6082)</td><td>5736</td><td>1</td><td>10,797.2</td><td><0.001</td><td>97.2* (83.4-99.9) NNT 100</td></tr>
<tr><td>Placebo (n=6075)</td><td>5766</td><td>66</td><td>10,881.5</td><td>0.3</td><td>—</td></tr>
</table>
NNT=100

<u>III. MITT-3 Analysis: HPV 16/18 related CIN 2/3, AIS or worse</u>
<table>
<tr><th></th><th>N</th><th>Cases (n)</th><th>Patient Years at risk</th><th>Incidence/100 pt-yrs at risk</th><th>Observed Efficacy (95% CI)</th></tr>
<tr><td>Vaccine (n=6082)</td><td>5947</td><td>68</td><td>11,159.5</td><td>0.6</td><td>40.9% (19.7-56.9) NNT 125</td></tr>
<tr><td>Placebo (n=6075)</td><td>5973</td><td>116</td><td>11,242.9</td><td>1</td><td>--</td></tr>
</table>
NNT-125

Immunogenicity is not included since data were not provided in the summary of FUTURE II received from the manufacturer.
</td>
<td></td>
</tr>
<tr>
<td>Villa 2006 [12]

R, DB, PC,</td>
<td>16-23 year old women who had participated in a</td>
<td>2-year extension to evaluate sustained</td>
<td>Two analyses were conducted: Per protocol efficacy analysis (PPE) (primary efficacy analysis) and modified intent to treat (MITT).</td>
<td>Adverse events were not discussed presumably since the</td>
</tr>
</table>

<table>
<tr>
<td>extension of Phase II study

N=241

2-year extension for total of 5 years</td>
<td>phase II dose-ranging study (ref 9). Women in the low dose vaccine and placebo groups (living in Brazil or Nordic countries) were invited to participate.</td>
<td>efficacy.

<u>Examinations for efficacy</u> ended at 36 months for the Phase II trial. Extension: began at 54 months and again at 60 months.

a) Gynecologic exam

b) cervicovaginal sampling for HPV DNA and Pap testing

c) Serological testing for anti-HPV antibodies (vaccine-specific)

<u>Primary Endpoints:</u>

Composite endpoint of persistent infection (2 or > times, tested 4 month apart) with vaccine HPV types or cervical or external anogenital or vaginal disease in the vaccine vs. placebo groups.</td>
<td>I. PPE-subjects who were PCR negative and seronegative to HPV 6/11/16/18 on day 1 and remained PCR negative to the same HPV-specific types (to which they were naïve upon enrollment) through month 7 after 3 vaccinations and did not violate the protocol.

II. MITT-subjects naïve to the relevant HPV type at enrollment and received at least one vaccination. Protocol violators were included.

<u>I. PPE Analysis: (n=overall cohort/extension cohort)</u>

Vaccine (n=277/114) Placebo (n=275/127)

<table>
<tr><th></th><th>N</th><th>Cases</th><th>Incidence/100 pt-yrs at risk</th><th>N</th><th>Cases</th><th>Incidence/100 pt-yrs at risk</th><th>Observed efficacy</th><th>95% CI</th></tr>
<tr><td>Primary Endpoint (infection or disease)</td><td>235</td><td>2</td><td>0.3</td><td>233</td><td>46</td><td>6.2</td><td>95.8%
NNT 5</td><td>83.8-99.5</td></tr>
<tr><td>Infection</td><td>235</td><td>2</td><td>0.3</td><td>233</td><td>45</td><td>6</td><td>95.6%
NNT 5</td><td>83.3-99.5</td></tr>
<tr><td>Disease</td><td>235</td><td>0</td><td>0</td><td>233</td><td>6</td><td>0.8</td><td>100%
NNT 38</td><td>12.4-100</td></tr>
<tr><td>CIN 1-3</td><td>235</td><td>0</td><td>0</td><td>233</td><td>3</td><td>0.4</td><td>100%
NNT 77</td><td><0-100</td></tr>
<tr><td>Condyloma</td><td>235</td><td>0</td><td>0</td><td>233</td><td>3</td><td>0.4</td><td>100%</td><td><0-100</td></tr>
<tr><td>HPV 6 related</td><td>214</td><td>0</td><td>0</td><td>209</td><td>17</td><td>2.4</td><td>100%</td><td>75.7-100</td></tr>
<tr><td>HPV 11 related</td><td>214</td><td>0</td><td>0</td><td>209</td><td>3</td><td>0.4</td><td>100%</td><td><0-100</td></tr>
<tr><td>HPV 16 related</td><td>199</td><td>1</td><td>0.2</td><td>198</td><td>28</td><td>4.4</td><td>96.6%</td><td>79.2-99.9</td></tr>
<tr><td>HPV 18 related</td><td>224</td><td>1</td><td>0.1</td><td>224</td><td>11</td><td>1.5</td><td>90.6%</td><td>35.6-99.8</td></tr>
</table>
*Data presented includes all women through 3 years in the Phase II trial and extension subjects through 2 additional years</td>
<td>vaccine was given 3 years earlier.

There was an 18-month period after the phase II trial ended and the extension began in which women were not monitored. The authors listed this as well as the small number of participants as a limitation to this study. Additionally, anti-HPV 18 GMTs did not appear to be statistically different between vaccinated and placebo recipients with prior natural infection with HPV 18.</td>
</tr>
</table>

II. MITT Analysis (n=overall cohort/extension cohort

	Vaccine (n=277/114)			Placebo (n=275/127)				
	N	Cases	Incidence/100 pt-yrs at risk	N	Cases	Incidence/100 pt-yrs at risk	Observed efficacy	95% CI
Primary Endpoint (infection or disease)	266	4	0.4	263	59	6.7	93.7% NNT 5	83-98.3
Infection	256	4	0.4	254	58	6.6	93.5% NNT 5	82.5-98.3
Disease	266	0	0	263	10	1	100% NNT 26	55.3-100
CIN 1-3	258	0	0	256	7	0.8	100% NNT 37	30.8-100
Condyloma	265	0	0	261	4	0.4	100%	<0-100
HPV 6 related	242	0	0	242	22	2.6	100%	81.9-100
HPV 11 related	242	0	0	242	4	0.5	100%	<0-100
HPV 16 related	225	3	0.4	229	34	4.4	91.6%	73.3-98.4
HPV 18 related	253	1	0.1	253	12	1.3	91.6%	43.3-99.8

Anti-HPV antibodies were measured and reported at months 7, 36 and 60. At month 60, anti-HPV geometric mean titers were remained above titers observed for women in the placebo recipients with a prior history of natural HPV infection. However, the differences for anti-HPV 18 antibodies at months 36 and 60 did not appear to be statistically different between vaccinated and those with prior natural exposure to HPV 18.

Abnl=abnormal, ADEs=adverse events, CIN=cervical intraepithelial neoplasia, DB=double-blind, MC=multicenter, P=parallel, PC=placebo-controlled, PCR=polymerase chain reaction, R=randomized, VaIN=vaginal intraepithelial neoplasia, VIN=vulvar intraepithelial neoplasia