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What is the safety and efficacy of vaccinating the male gender to prevent HPV related neoplastic disorders in both the male and female genders?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies

Philadelphia College of Osteopathic Medicine

Philadelphia, Pennsylvania

December 15, 2010

Abstract

Objective: To determine the safety and efficacy of vaccinating the male gender to prevent HPV related neoplastic disorders in both the male and female genders.

Study Design: Review of all randomized controlled trials and comparative studies in the English language from the time periods of 2000 to 2009.

Data Sources: Two RCT's and one comparative study was found using PubMed, Ovid, Cochrane database of Randomized Control Trials, and Cochrane database of Systematic Reviews.

Outcomes Measured: Outcomes were measured for safety and efficacy. Outcomes were based upon a vaccination report card (VRC) and proven immunity to the HPV types being studied. Participants were given a scale and asked to rate their symptoms based upon mild, moderate, or severe. "Mild" was defined as awareness of signs or symptoms, but easily tolerated; "moderate" was defined by discomfort enough to cause interference with usual activities; and "severe" was incapacitating with the inability to work or do usual activities (Block).[1] Titer levels were drawn to associate immunogenicity within the participants. Numeric values of titer levels however are not POEM based. What is POEM based is whether or not these patients will be able to know that they are protected from contracting or transmitting HPV 6/11/16/18 and related neoplasm's.

Results: Two RCT's and one comparative study were included in this review. All three of the studies proved safety and efficacy of either the quadrivalent or bivalent HPV vaccine. Very few serious adverse events (SAEs) were contributed to the vaccination. Only 1 SAE was said to be vaccination related. Immunogenicity was proved to be non-inferior to girls and women in all 3 studies.

Conclusions: The Block study, the Petaja study, and the Reisinger study all show that the HPV vaccine is overall safe and effective for the male population.

Key Words: HPV vaccine; Gardisil; Cervarix, Boys

Introduction

Human Papillomavirus (HPV) infections are responsible for causing neoplasms in both the male and female genders. There are more than 100 HPV viruses, and around 30 out of these 100 are passed through sexual contact. HPV infections are divided into two groups; low risk and high risk. The low risk types are known to be HPV types 6 and 11; the high risk types are known to be HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 73. The high risk category is known to be oncogenic or carcinogenic. HPV infections are common with a lifetime risk exceeding 50% for both males and females.[3] HPV is a major cause of cervical and anogenital cancers; therefore the high prevalence of genital HPV infection is considered a serious worldwide health issue.[3] Due to the well-established link between HPV and anogenital cancers, genital warts, and low/high grade dysplasia, there is now a prophylactic vaccine available for the four most common types of low and high risk HPV. The quadrivalent vaccine was approved in 2006 and first available only to females; this vaccine is now extended to males after FDA approval in October 2009.[6]

Worldwide, greater than 500,000 cases of cervical and other genital cancers are caused by HPV infection annually, with greater than 273,000 deaths attributable to cervical cancer.[1] Studies have shown that the first 5 years following sexual debut represents the period of highest risk for acquisition of HPV infection.[3] An estimated annual cost for HPV related neoplasms in the year 2000 for ages 15-24 was $2.8 billion for women, and $62 million for men.[5] In most countries the median/mean age of a primary sexual experience occurs between 15 and 16 years of age.[3] Studies have also proved that oral HPV infection is a strong risk factor for oropharyngeal cancer. Researchers found that an oral HPV infection and past HPV exposure

increase the risk of oropharyngeal of squamous cell cancer regardless of tobacco and alcohol use.[4] Therefore it is important that the vaccine be extended to both male and female genders, offering HPV cancer prophylaxis and prevention to both sexes. Extending the vaccine to both males and females can help to decrease transmission of the HPV virus regardless of one’s gender or sexual preference.

Gardisil is a quadrivalent 3 dose regimen vaccine that protects against HPV types 6, 11, 16, and 18. It has been proven to be highly protective and effective when given to females. Gardisil was FDA approved for the male gender in 2009, after studies showed proven effectiveness and immunogenicity in the male gender. Another HPV vaccine on the market is under the name of Cervarix. This is a bivalent vaccine offering protection against HPV types 16, and 18. At this time Cervarix is only FDA approved and indicated for the female gender. The highest risk of acquiring HPV infection is within the first 5 years after sexual debut, and because of this, the HPV prophylactic vaccination against would have the greatest benefit in sexually naïve adolescents.[3] The quadrivalent vaccine is however now approved and indicated for males and females 9-26 years of age, regardless of their sexual preference or number of sexual partners.

Objective

The objective of this systematic review is to determine whether “It is safe and effective to vaccinate the male gender to prevent HPV related neoplastic disorders in both the male and female genders?” Recent approval of Gardisil does indicate safety and efficacy in boys and men 9 through 26 years of age for the prevention of genital warts (condyloma acuminata) caused by HPV types 6 and 11. The FDA did not indicate the use of Gardisil in the male gender to help

protect or prevent the transmission of HPV types 16, and 18.

Methods

A detailed search was completed by the author of this review using the advanced search engine of PubMed, Ovid, Cochrane database of Randomized Control Trials, and Cochrane database of Systematic Reviews. Key words in this research search were: Boys, Gardisil, HPV, and HPV Vaccine and Males. This combination search was done and limits were placed for published articles written in the English language from the time period of 2000 to 2009. The criteria used for the selection of studies focused on the male population ages 9 to 26. Administration of the HPV vaccine was the intervention; compared to those who received a placebo vaccine, or injection of saline. Articles that were selected were based on Patient Oriented Evidence that Matters (POEM). Outcomes were based upon the safety and tolerability of the vaccine as measured by the patient, and whether or not the vaccine would prevent the patient from having cancerous or neoplastic HPV (patient oriented evidence that matters). Clinically, titers were drawn to prove the level of immunogenicity that the males would retain by receiving the HPV vaccine, and also proving that males were non-inferior to females with immunogenicity to the quadrivalent or bivalent HPV vaccine. The actual numeric value of the titer levels are not considered POEM based because the antibody response is not something that the patient cares about; however, it is the method clinically that researchers can use to prove immunogenic response. Out of the three studies that were included; one was a comparative study and the other two were randomized controlled trials. Two of the studies were double blinded and the third study was observer blinded. The results of these demographics are displayed in **Table 1** along with the description of inclusion and exclusion criteria for the individual studies. All three studies focused on the safety and efficacy of either the bivalent or

quadrivalent vaccine within the male population. **Table 1**

Study	Type	# of Pt's	Age in Years	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Block 2006	Comparative Study Randomized Double-Blinded	1,529	10-15 Male and female 16-23 Female Only	Healthy boys and girls that were sexually naïve before and during the study. For the older population of females only, they were required to be generally healthy, have an intact uterus, with no evidence of cervicitis.	Allergy to any vaccine component; if they had recvd blood or components within the past 6 mos.; had any known immune or coagulation disorder; had recvd any vaccine product within 14 days before enrollment or any live vaccine product 21 days before enrollment. The older females aged 16-23 were excluded if they had HX of genital warts, abnormal pap, HX of CIN, or > 4 lifetime sexual partners.	2	Quadrivalent HPV vaccine 6/11/16/18; this was administered to both male and female populations to compare immune response.
Reisinger 2007	RCT Observer Blinded	1,781	9-15	Healthy boys and girls that were sexually naïve going into the study.	Similar to that described for a non-inferiority immunogenicity bridging study. [3]	6	Quadrivalent HPV vaccine 6/11/16/18; vs. saline placebo.
Petaja 2009	RCT Double-Blinded	270	10-18	Healthy boys.	Use of an investigational drug or vaccine within 30 days; use of immune modifying drugs within 6 mos; blood or products within 3 mos; previous vaccine of HBV or HPV; active/past HBV infection; HIV.	8	HPV 16/18 AS04-adjuvanted vaccine vs. the HBV control vaccine.

Outcomes Measured

All 3 studies maintained a congruent approach to measure the safety and tolerability of the vaccine. The participants were observed for at least 30 minutes after each vaccination for any immediate reaction. Oral temperatures were recorded for 5 days following each injection. The method that participants used to track their local or systemic adverse advents (AEs) is known as a vaccination report card (VRC). Adult participants maintained a VRC themselves post vaccination; and the VRC for adolescent participants were tracked by their parent/guardian. Participants were given a scale and asked to rate their symptoms based upon mild, moderate, or severe. “Mild” was defined as awareness of signs or symptoms, but easily tolerated; “moderate” was defined by discomfort enough to cause interference with usual activities; and “severe” was incapacitating with the inability to work or do usual activities (Block).[1]

The other outcome measured regarding a POEM based patient perspective is, do those patients now have the protection from receiving or transmitting HPV related neoplasms? Although the titer levels do show immunity, that is not something that a patient can gauge from his or her perspective. However, the patient can gauge whether or not they have or can transmit cancerous growths to their anogenital region.

Results: Tables 2-7 to include all three separate studies.

Table 2 and **Table 3** Study on Comparison of the immunogenicity and Reactogenicity of Prophylactic Quadrivalent HPV (Types 6, 11, 16, and 18) L1 Virus-Like Particle Vaccine in Male and Female Adolescents and Young Adult Women.

Table 2: Safety Across all 3 series of vaccinations

	Girls	Boys	Women
	n/%	n/%	n/%
Participants follow-up	501	500	497
Vaccine AEs	423/84.4	396/79.2	444/89.3
Injection site AEs	405/80.8	370/74.0	435/87.5
Systemic AEs	154/30.7	136/27.2	160/32.2
Serious AEs	1/0.2	1/0.2	0/0.0

Table 3: Efficacy; Non-inferiority of GMTs in Girls and Boys Vs Women at Month 7

	Girls	**Boys**	**Women**	**GMT Ratio (95% CI)**	**GMT Ratio (95% CI)**
Assay (cLIA)	**n/GMT[a] (mMU/ml)**	**n/GMT[a] (mMU/ml)**	**n/GMT[a] (mMU/ml)**	**Girls/Women**	**Boys/Women**
Anti-HPV6	423/959	428/1042	320/575	1.67[b] (1.46-1.91)	1.81[b] (1.58-2.08)
Anti-HPV11	423/1220	428/1318	320/706	1.73[b] (1.50-2.00)	1.87[b] (1.60-2.17)
Anti-HPV16	424/4697	427/5638	306/2548	1.84[b] (1.54-2.20)	2.21[b] (1.84-2.66)
Anti-HPV18	426/916	429/1212	340/453	2.02[b] (1.71-2.39)	2.68[b] (2.24-3.19)

[a] Based on a statistical model adjusting for region.
[b] Noninferiority P< .001

Table 4 and **Table 5** is the Immunogenicity and Safety of HPV 16/18 AS04-Adjuvanted Vaccine in Healthy Boys Aged 10-18 Years

Table 4 Safety and Tolerability of the HPV vaccine vs. Placebo

		HPV 16/18 N=523		**HBV N=259 Control**	
Symptom	**Type**	**n (%)**	**(95% CI)**	**n (%)**	**(95% CI)**
Pain	**All**	378 (72.3)	(68.2, 76.1)	57 (22.0)	(17.1, 27.6)
	Grade3[a]	10 (1.9)	(0.9, 3.5)	0 (0.0)	(0.0, 1.4)
Redness	**All**	87 (16.6)	(13.5, 20.1)	29 (11.2)	(7.6, 15.7)
	>50mm	0 (0.0)	(0.0, 0.7)	0 (0.0)	(0.0, 1.4)
Swelling	**All**	56 (10.7)	(8.2, 13.7)	8 (3.1)	(1.3, 6.0)
	>50mm	2 (0.4)	(0.0, 1.4)	1 (0.4)	(0.0, 2.1)

N= number of documented doses (with safety diary cards returned)
CI= exact confidence interval; n (%) = number/percentage of doses that were followed by at least one symptom.
[a] Pain that prevented normal activity.

Table 5 Immunogenicity Table[2]; GMT's for HPV 16 and 18 antibodies in initially seronegative boys aged 10 to 18 years at month 2 and month 7

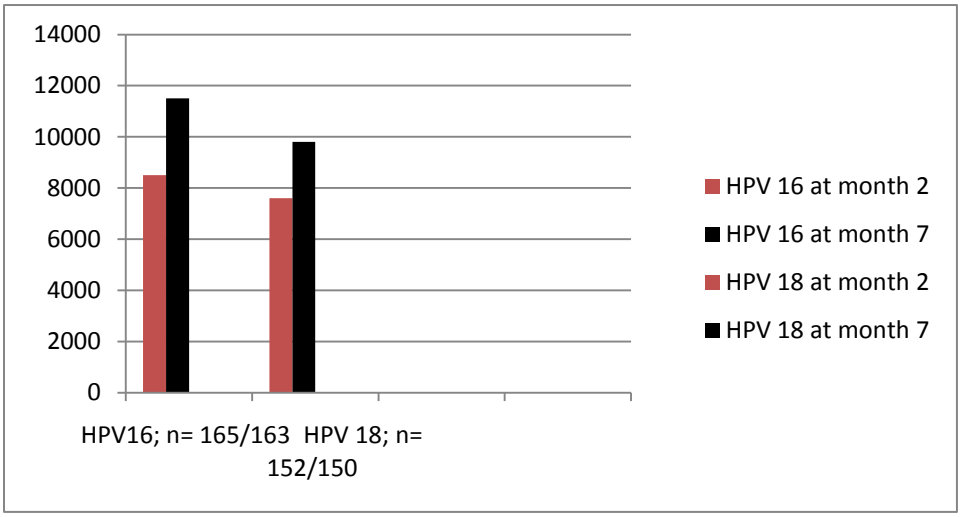

Table 6 and **7 study on the Safety and Persistent Immunogenicity of the Quadrivalent Vaccine in Preadolescents and Adolescents**

Table 6 Safety and Adverse Experience Summary Across all 3 series of vaccines

	Vaccine	**Non-aluminum Placebo**
# of subjects w/ Follow-up	1165	584
1 or more AE	963 (82.7)	392 (67.1)
Injection-site AE	877 (75.3)	292 (50.0)
Erythema	237 (20.3)	77 (13.2)
Pain	853 (73.2)	265 (45.4)
Swelling	241 (20.7)	45 (7.7)
Systemic AE	541 (46.4)	260 (44.5)
With serious AE	5 (0.4)	0 (0.0)
Fever; total number affected	1157	579
<100 degrees F or normal	1074 (92.8)	541 (93.4)
≥100 degrees F	83 (7.2)	38 (6.6)

Table 7 Analysis of Month 7 Anti-HPV Responses for HPV Types 6/11/16/18

Parameter	**Boys**		**Girls**		**Difference/Fold Difference (95% CI)***
	n	**Response**	**n**	**Response**	
Anti-HPV 6 %Seroconversion	456	99.8	492	99.8	0.0 (-1.0, 1.0)
GMT (mMU/mL)		1007		808	1.3 (1.0, 1.5)
Anti-HPV 11 %Seroconversion	457	99.8	492	99.8	0.0 (-1.0, 1.0)
GMT (mMU/mL)		1334		1187	1.1 (0.9, 1.4)
Anti-HPV 16 %Seroconversion	455	99.5	489	99.8	-0.2 (-1.4, 0.8)
GMT (mMU/mL)		6316		4490	1.4 (1.1, 1.8)
Anti-HPV 18 %Seroconversion	458	99.8	494	99.6	0.2 (-0.8, 1.3)
GMT (mMU/mL)		1581		1071	1.5 (1.2, 1.9)

*Difference = Boys minus girls; Fold difference = boys divided by girls. $P < 0.001$ for all tests of noninferiority of immune response in boys to those in girls (for all 4 vaccine HPV types for both endpoints).

Results

The main point out of these three studies is to hypothesize whether or not it is safe and effective to vaccinate the male gender with a HPV vaccine. In **Table 2** and **Table 3**, the Block study shows a comparison of immune response as well as safety of the vaccine in adolescents as compared to women ages 16-23. The table provided includes all of the three groups of participants and averages the outcome of tolerability and safety. The 3 dose regimen of the HPV vaccine was overall well tolerated. The most commonly reported systemic adverse events were headache (23.2%) and fever (13.1%).[1] The majority of the injection site reactions

were mild to moderate, characterized by redness and swelling. The first dose of the three dose regimen was reported to carry the most complaints for redness and swelling. There were three serious adverse events, 2 of them were proved to be unrelated to the vaccine; a cardiac ventricular arrhythmia, and the second serious AE was an intentional overdose on chlorpheniramine tablets and homeopathic arsenicum. The third serious AE was deemed to be vaccine related by the reporting Physician; this participant was a 13 year old girl affected with a vaginal hemorrhage 26 days post-dose 2 of the HPV vaccine.

Table 3 shows that the male population was non-inferior to immunogenicity of the girls and woman at the 7th month; titers drawn 4 weeks after the 3rd dose of the vaccination regimen. The end points of the study were the geometric mean titers (GMTs) of neutralizing antibodies for each HPV type.[1] The sample size of the study was chosen to provide >99% power to declare noninferiority in immunogenic responses and seroconversion rates for at least 1 of the populations (girls or boys compared with women) (Block).[1] Therefore, turning this data into POEM data, males are just as protected as females are from HPV after receiving the HPV vaccine.

Table 4, Table 5, Table 6, and **Table 7** show the same type of information as described in **Table 2 and Table 3. Table 4** does show that there were more AE's of local and systemic reactions with the HPV and compared to the placebo HBV vaccine. The Petaja study does mention however that the solicited local symptoms did not affect compliance with the vaccination, as evidenced by 97% of the boys in both vaccine groups completed the three dose vaccination course.[2] As shown in **Table 5**, the immune response in boys aged 10 to 18 years in this study was noninferior for both seroconversion rates and GMTs to that seen in women aged 15 to 25 years in the historic comparator study, an age range in which a high

degree of protection against HPV 16/18 infection and associated cervical lesions has been shown (Petaja).[2] Again, POEM based data is that males are as protected as females after receiving the vaccine.

Tables 6 and **7** are much like that of the study of **Tables 2** and **3**. It is mentioned in the study that 5 serious adverse events were reported through month 18, all of which occurred among the quadrivalent HPV vaccine recipients, and were judged by the investigator to be not vaccine related. As in the previous study, infection site adverse experiences were greater than placebo but few participants discontinued the vaccination series because of the AEs. **Table 7** shows that for each of the 4 vaccine types, ≥99.5% of the subjects in the respective per-protocol immunogenicity cohort had seroconverted by 1 month after completion of the 3-dose regimen, regardless of their gender (Reisinger).[3]

Discussion

The two RCTs and one comparative study showed overall that the quadrivalent and the bivalent HPV vaccine was safe and effective in preventing HPV and HPV related neoplasms. There were adverse events that occurred within the HPV population greater than that within the placebo, however, most of the events were consistent with local injection site redness and soreness, and systemic reactions of either headache or fever. Most of these adverse events were tolerated and discontinuance due to AEs of the vaccine regimen was a rarity. Immunogenicity of the said HPV strains was proved by titer levels.

Conclusion

The antibody response of the HPV vaccine was shown to be noninferior to the studies done in girls and women. The HPV vaccine was also proved to be overall safe with few minor

immediate local and systemic side effects. Statistically, studies have shown that the first 5 years following sexual debut represents the period of highest risk for acquisition of HPV infection.[3] Therefore, immunizing males and females before their sexual debut becomes important to prevent receiving and transmitting HPV. Thus stating, the vaccine should be targeted towards adolescents and preteens. As mentioned in the introduction, an estimated annual cost for HPV related neoplasms in the year 2000 for ages 15-24 was $2.8 billion for women, and $62 million for men.[5] It can only be assumed that in the year 2010, the incidence has increased. Given those statistics, it is clear that HPV affects and takes lives of many individuals. HPV infection is common in men and is readily transmitted influencing disease rates in both men and woman (Petaja).[2] The findings of safety and immunogenicity of the HPV vaccine in the male population definitely lend support to the implementation of a gender neutral vaccine to prevent widespread morbidity and mortality from HPV related cancers, as well as dysplastic cervical and external genital lesions affecting the general population. The limitations to this study include long term immune response which would necessitate the need for a booster vaccine.

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