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Gardasil™ HPV vaccination: Surveillance of vaccine usage and adherence in a military population☆,☆☆,★

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ABSTRACT

Objectives. To investigate the usage patterns and adherence rates with the quadrivalent HPV (qHPV) vaccine at Naval Medical Center San Diego.

Methods. This retrospective, cross-sectional study was conducted by using AHLTA (Electronic Health Record of DoD) to identify all qHPV recipients between 2006 and 2009. Charts were reviewed to extract demographic variables and immunization schedules for association analysis. Subjects were assigned intention-to-treat (ITT) if they initiated the series and reached the 1-year anniversary after dose-1 or in-progress (IP) if the series was incomplete and within 1-year. ITT subjects were designated non-adherent or adherent based on 1–2 or 3 doses received.

Results. 6792 females and 46 males with respective mean ages (years) of 19 (95% CI: 10–29) and 27 (95% CI: 9–46) initiated the qHPV series. The evaluable ITT population consisted of 5088 females and 31 males. The adherence rate for females was 32% (1656/5088) versus 3% (1/31) for males. For females, adherence declined from 45%, 24%, to 14% with respect to increasing age: 8–17, 18–26, 27–50 years. Adherence declined accordingly by beneficiary status: dependent daughters (43%), spouses (21%) and active duty (16%); and by clinic of vaccine initiation: Pediatrics/Adolescent (45%), Primary Care (38%), Immunization (21%), and OB/GYN (9%). Males were predominantly active duty 84%, vaccinated through immunization clinics 84%, and poorly adherent 3%.

Conclusions. Optimal HPV immunization efficacy is derived from vaccine adherence and HPV naivety. This study of qHPV adherence has provided insight into real-world suboptimal use post-marketing. Usage patterns and adherence rates were significantly associated with demographic characteristics.

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Introduction

On June 8, 2006, the United States Food and Drug Administration (FDA) announced the approval of Gardasil™ HPV vaccine for licensure [1]. It was the world's first vaccine developed to prevent human papillomavirus (HPV) infections and associated diseases. The vaccine was brought to market after years of collective research by multiple institutions around the world to include the University of Rochester, Georgetown University, Queensland University in Australia, the U.S. National Cancer Institute, and Merck & Co. [2]. Since licensure, Gardasil™ has been approved in 123 countries with over 50 million doses distributed worldwide [3,4]. In the United States alone, 33 million doses have been distributed but the actual administered doses are unknown [5].

Initially approved for females between the ages of 9 and 26 in the United States, the indications for Gardasil™ have expanded and evolved over the last 5 years [6]. On October 16, 2009, the FDA extended the vaccine indication to include boys and men ages 9–26 for the prevention of genital warts caused by HPV types 6 and 11 [7,8]. Then on December 22, 2010, the FDA again broadened the indication to include prevention of anal intraepithelial lesions and cancer [9]. Most recently, the safety and immunogenicity profile of the vaccine in women ages 27–45 was added to the product information [10,11]. Prior to FDA approval, select physicians administered the vaccine off-label to men engaged in high-risk sexual behavior.

The quadrivalent vaccine (qHPV) manufactured by Merck & Co. (Whitehouse Station, NJ) is based on virus-like particles (VLPs) assembled from recombinant HPV capsid proteins that are antigenic

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★ CONDENSATION: This study of HPV vaccine adherence has provided insight into real world suboptimal use after marketing.

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for HPV-6/11/16/18 [12]. The approval of the vaccine was based on multiple studies that documented its efficacy [7–14]. Specifically, the Per-Protocol-Efficacy against cervical intraepithelial neoplasia (CIN2+) and condylomata and anal lesions in males were 98%, 89% and 78%, respectively. However, the intention-to-treat efficacy (recipient of at least 1 dose and regardless of serology and genital HPV DNA status to qHPV types) dropped significantly for the respective lesions: 44%, 67%, and 50% [7–14]. These studies and others indicate that the greatest efficacy is derived from vaccine adherence and maintenance of HPV naivety throughout the vaccination period.

Currently, the U.S. national qHPV usage patterns and adherence rates since licensure are not explicit. The only glimpse is offered by the CDC's National Immunization Survey-Teen (NIS-Teen) initiated in 2006 to estimate vaccination coverage from a national sample of adolescents aged 13–17 years [15,16]. Among adolescent girls surveyed in 2007 (n = 1440) and 2008 (n = 8607), the percentage of those who initiated the vaccine series increased from 25.1% to 37.2%. However, the 3-dose completion rate (only available for the 2008 recipients) was 48.1% [16]. This preliminary national statistic suggests "real-world" qHPV adherence rates may be underwhelming with compromised efficacy.

From clinical trials, qHPV has demonstrated superb efficacy under controlled, per-protocol conditions. However, vaccine adherence in the general female population as reported by a handful of academic medical centers suggests considerable incompletion rates [17–19]. This cross-sectional study was undertaken to determine the post-marketing qHPV adherence rates in the unstudied U.S. military population. We aimed to investigate all qHPV recipients, regardless of age, gender, or status to avoid exclusion bias and to gain insight to qHPV utilization among medical specialties. Secondarily, vaccine usage characteristics and patterns were gleaned to examine its association with adherence.

Materials and methods

Approval to conduct this study was obtained from the Institutional Review Board of Naval Medical Center San Diego (NMCSD), California. A retrospective, cross-sectional study was conducted by using AHLTA (Electronic Medical Record of the Department of Defense), to search for patients who received qHPV vaccination at NMCSD and its affiliated clinics from July 2006 to April 2009. The following Current Procedural Terminology (CPT) and Diagnosis codes: 90649 (HPV vaccine) and V04.89 (need for prophylactic vaccination and inoculation against; other viral diseases) were used to generate the listing of patients. The time period chosen marked the initiation of qHPV vaccination at NMCSD to data collection. After patient identification and verification of vaccination, an electronic chart review was performed to extract variables of interest: demographics (age, gender, and military/beneficiary status), clinic of origination by specialty, and vaccination schedules. Specifically, the qHPV vaccination data for each subject was recorded as CPT code 90649 with accompanying date, dosage and site of administration. If the date of the 1st dose was in question, a detailed review of the clinician's progress note in AHLTA and/or calculation of dosing interval (2 versus 4 months between the 1st and 2nd or 2nd and 3rd doses) assisted in assignment of proper dose order. Patients were not contacted for additional clinical information.

We analyzed the receipt of the qHPV doses according to the dose and schedule recommended by the Advisory Committee on Immunization Practices (ACIP) [12]. The timeframe permitted for completion of the 3-dose series is 1 year as defined in the FUTURE II trial [13]. Timeliness of immunization was defined as the recommended schedule at month 2 ± 1 month and month 6 ± 2 months. This was based on the anti-HPV immunogenicity profile of 18–26 year-old women derived from Merck sponsored clinical trials which showed timing flexibility (detailed above) did not adversely impact the immune responses to Gardasil™ [20]. Of note, this is in contradistinction to childhood immunizations which generally defines "delayed" vaccination as inoculation 4 weeks past the recommended age range [21,22]. For subject allocation, we applied the intention-to-treat principle which is an analysis based on initial treatment intent, not on eventual treatment administered. Hence, the intention-to-treat (ITT) subjects were defined as those who initiated the vaccine series and reached the 1-year anniversary after dose #1 (regardless of receipt of doses 2 or 3). Patients who had not completed the 3-dose series, but still within the 1-year timeframe for completion were defined as in-progress (IP) subjects. The ITT subjects were further categorized as "non-adherent" or "adherent" to the 3-dose regimen based on 1–2 or 3 doses received, respectively.

Naval Medical Center San Diego is composed of a large multi-specialty medical center with 10 branch clinics. A total of 49 separate "clinic type" codes were identified by the visits of the vaccinated subjects. For simplicity of systemization, these clinics were grouped into 4 broad medical specialties, i.e. Pediatrics/Adolescent, Primary Care, Immunization, and Obstetrics/Gynecology which served as each subject's clinic of qHPV initiation.

Data were summarized using means (95%), medians (IQR), and proportions. Odds and odds ratios were calculated as a measure of association between predictor and outcome variables. The odds-of-vaccination was defined as the probability that the event will occur to the probability that the event will not occur ($Odds = P/1–P$). In this study, the group with the highest odds (probability of receiving the dose than not) was used as the reference group within each demographic category (age group, beneficiary status, and clinic specialty). Categorical variables were compared using the χ^2 test or Fisher's exact test as appropriate. P values < 0.05 were regarded as significant. All statistical analyses were performed with statistical software STATA 11/IC (StataCorp LP, College Station, TX).

Results

A total of 6838 patients initiated the qHPV vaccine during the study period. The study population was predominantly female (n = 6792) with a mean age of 19 years (95% CI: 10 to 29) (Supplementary Fig. S1). The male population constituted only 46 patients with a mean age of 27 years (95% CI: 9 to 46) (Supplementary Fig. S1). After assignment of the total population to either the ITT or IP groups, further analysis was conducted after excluding IP patients (female: n = 1704; male: n = 15). The remaining 5088 female ITT subjects emerged as the focus of our analysis and results in contrast to the data derived from the small subset of male ITT subjects (n = 31).

For the female population, the details of the demographic data and vaccine adherence rates by dose number are presented in Table 1. Of the cohort who initiated the vaccine series, 5088/6792 subjects (75%) reached the 1-year anniversary and was deemed evaluable. Vaccine adherence declined precipitously for the 2nd dose (2879/5088 subjects (56.6%)) to the 3rd dose (1656/5088 subjects (32.5%)), (χ^2, $P<0.001$). The adherence rate (3-doses) also declined with increasing age (Fig. 1). After segregating the ITT subjects into 3 age groups (8–17, 18–26, 27–50 years), the respective adherence rates for the 3rd dose were (959/2146 (45%), 676/2794 (24%), 20/148 (14%), (χ^2, $P<0.001$)). Beneficiary status was also found to be associated with adherence. The 3-dose completion rates declined significantly (χ^2, $P<0.001$) from dependent daughters 43% (1265/2924) to dependent spouses 21% (157/740); the least adherent group was active duty women with a 16% (233/1424) completion rate. The majority of patients at the time of vaccine initiation originated from the Primary Care (46%), and Pediatrics/Adolescent Clinics (24%). The adherence rates by clinic specialty in descending order were as follows: Pediatrics/Adolescent 45% (541/1205), Primary Care 38% (889/2317), Immunization 21% (153/732), and Obstetrics/Gynecology 9% (73/834), (χ^2, $P<0.001$). Among the 3 demographic categories, the groups that demonstrated the highest 2nd and 3rd dose adherence rates (χ^2, $P<0.001$) were age group

Table 1
Female population: qHPV vaccine adherence by demographic characteristics.

Demographic category	Dose-1		Dose-2				Dose-3			
	n	(%)[a]	Yes	No	Odds	OR (95% CI)[b]	Yes	No	Odds	OR (95% CI)[b]
			n	*n*			*n*	*n*		
Vaccination status										
Total	6792	(100)								
Intent-to-vaccinate	5088	(75)	2879	2209	1.30	–	1656	3432	0.48	–
In-progress	1704	(25)	646	1058	0.61	–	–	–	–	–
Age group[c] (years)										
08–17[d]	2146	(42)	1526	620	2.46	Referent[d]	959	1187	0.81	Referent[d]
18–26	2794	(55)	1315	1479	0.89	0.36 (0.32–0.41)[e]	676	2118	0.32	0.40 (0.35–0.45)[e]
27–50	148	(3)	38	110	0.35	0.14 (0.09–0.21)[e]	20	128	0.16	0.19 (0.11–0.31)[e]
Beneficiary status[c]										
Dependent daughter[d]	2924	(57)	2024	900	2.25	Referent[d]	1265	1659	0.76	Referent[d]
Dependent spouse	740	(15)	313	427	0.73	0.33 (0.28–0.39)[e]	157	583	0.27	0.35 (0.29–0.42)[e]
Active duty	1424	(28)	542	882	0.61	0.27 (0.24–0.31)[e]	233	1191	0.20	0.26 (0.22–0.30)[e]
Clinic specialty[c]										
Peds/Adolescent[d]	1205	(24)	856	349	2.45	Referent[d]	541	664	0.81	Referent[d]
Primary Care	2317	(46)	1476	841	1.76	0.72 (0.61–0.83)[e]	889	1428	0.62	0.76 (0.66–0.88)[e]
Immunization	732	(14)	333	399	0.83	0.34 (0.28–0.41)[e]	153	579	0.26	0.32(0.26–0.40)[e]
Obstet/Gynecol	834	(16)	216	618	0.35	0.14 (0.12–0.17)[e]	73	761	0.10	0.12 (0.09–0.15)[e]

Note. Dose-1, -2, -3 = 1st, 2nd or 3rd dose of qHPV vaccine received by individual subjects within the 1-year timeframe since initiation. Yes or No indicates receipt or non-receipt of the specified dose.

[a] Percentage of subjects in each demographic category.
[b] OR and 95% CI for the proportional difference in specified dose received between the referent and other groups within the same category.
[c] The total number ($n = 5088$) in the demographic categories was derived from the intention-to-treat (ITT) population.
[d] Referent group for calculation of odds ratio. It is the group with the highest odds of receiving the specified dose in the demographic category.
[e] $P<0.001$, by χ^2 test.

8–17, dependent daughters, and Pediatrics/Adolescent Clinic population.

Timeliness of vaccination by female ITT subjects was also determined. The median days from the initial dose to receiving dose-2 was 76 (interquartile range, 62–136) and for dose-3 197 (interquartile range, 182–245). For dose-2 recipients 1159/2879 (40%) received delayed inoculation (3 months past vaccine initiation); whereas, 450/1656 (27%) dose-3 recipients delayed the inoculation past the 8 month mark.

For the male population, the details of the demographic data and vaccine adherence rates by dose number are presented in Table 2. Of the male ITT subjects (n = 31), most were active duty 26/31 (84%), vaccinated through immunization clinics 26/31 (84%), and poorly adherent 1/31 (3%). Due to the small sample size and poor adherence among all demographic categories, interpretation of the data is limited and ineffectual. However, it is notable that certain demographic groups exhibited higher adherence rates than others, i.e. age group 12–17, dependent sons, and Pediatrics/Adolescent Clinic population.

Discussion

Our study was conducted at a large naval medical center in Southern California. The institution is comprised of multi-specialty clinics onsite and numerous outlying clinics. The results of our study revealed a high rate of usage of qHPV among various clinics since July 2006. Disappointingly, the overall 3-dose adherence rate among females who initiated the vaccine was relatively low (32%). The highest adherence rates (~45%) were achieved in the female population within the adolescent, dependent

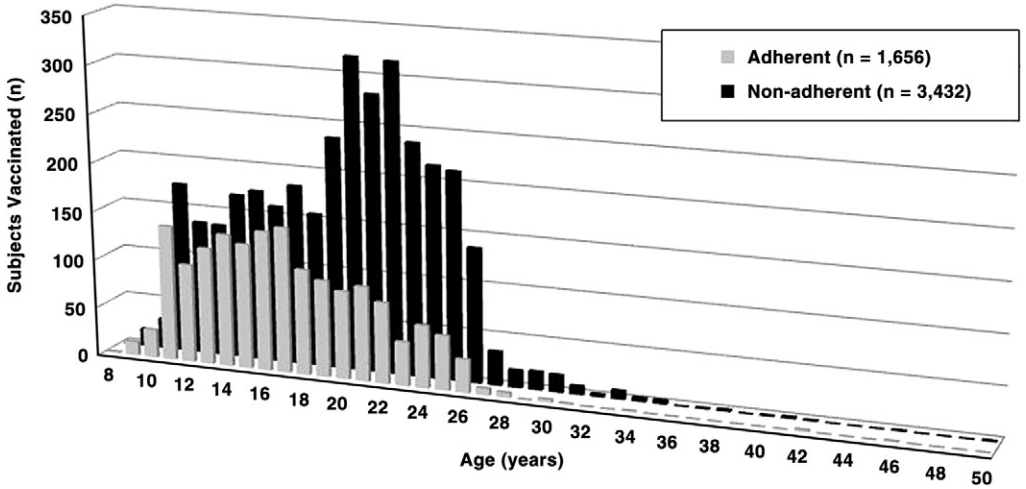

Fig. 1. Female intention-to-treat population stratified by qHPV adherence and non-adherence. Non-adherence or adherence to the 3-dose regimen was based on 1–2 or 3 doses received, respectively. Adherence declined significantly with increasing age.

Table 2
Male population: qHPV vaccine adherence by demographic characteristics.

Demographic category	Dose-1		Dose-2				Dose-3			
	n	(%)[a]	Yes	No	Odds	OR (95% CI)[b]	Yes	No	Odds	OR (95% CI)[b]
			n	*n*			*n*	*n*		
Vaccination status										
Total	46	(100)								
Intent-to-vaccinate	31	(67)	2	29	0.07	–	1	30	0.03	–
In-progress	15	(33)	3	12	0.25	–	–	–	–	–
Age group[c] (years)										
12–17[d]	5	(16)	1	4	0.25	Referent[d]	1	4	0.25	Referent[d]
18–26	16	(52)	0	16	0	0	0	16	0	0
27–51	10	(32)	1	9	0.11	0.44 (0.005–43.5)[e]	0	10	0	0
Beneficiary status[c]										
Dependent son[d]	5	(16)	1	4	0.25	Referent[d]	1	4	0.25	Referent[d]
Active duty	26	(84)	1	25	0.04	0.16 (0.002–15.7)[e]	0	25	0	0
Clinic specialty[c]										
Peds/Adolescent[d]	2	(6)	1	1	0.50	Referent[d]	1	1	0.50	Referent[d]
Primary Care	3	(10)	0	3	0	0	0	3	0	0
Immunization	26	(84)	1	25	0.04	0.04 (0.0005–6.3)[e]	0	26	0	0

Note. Dose-1, -2, -3 = 1st, 2nd or 3rd dose of qHPV vaccine received by individual subjects within the 1-year timeframe since initiation. Yes or No indicates receipt or non-receipt of the specified dose.

[a] Percentage of subjects in each demographic category.

[b] OR and 95% CI for the proportional difference in specified dose received between the referent and other groups within the same category.

[c] The total number ($n = 31$) in the demographic categories was derived from the intention-to-treat (ITT) population.

[d] Referent group for calculation of odds ratio. It is the group with the highest odds of receiving the specified dose in the demographic category.

[e] $P > 0.05$, by exact test.

children, and Pediatrics/Adolescent Clinic categories. In contrast, the lowest adherence rates (<16%) were noted in the adult, active duty women and those attending the Obstetrics and Gynecology clinic.

In regards to timeliness of vaccination, the majority of motivated subjects who received the 2nd and/or 3rd doses achieved this within the confines of the recommended schedule. Counterintuitive to expectations, a greater proportion of the 2nd versus 3rd dose was received as delayed inoculation. In general, a lapsed vaccination schedule does not reduce final antibody levels; instead protection may be stalled until completion of all doses [23]. In other words, a lengthy delay of the 3rd dose may temporize instead of annul the desired immune response. Zimmerman et al. demonstrated that an alternative qHPV schedule at 0, 2, and 12 months to be non-inferior to the standard schedule by comparing anti-HPV type-specific titers [24]. However, clinical outcomes were not ascertained. Consequently, the efficacy of the alternative regimen, likewise a "delayed regimen" remains unknown.

Our data on boys and men were limited by small numbers and wide confidence intervals around point estimates. Hence it is difficult to deduce any meaningful generalizations. However, two observations are noteworthy of comment. First, only 1/31 (3%) ITT subjects finished the 3-dose regimen. The rationale behind the overall poor adherence was not a subject of this study but is highly concerning for future vaccine effectiveness in the male population-at-large. Second, the majority of males 26/31 (84%) received their vaccine directly through immunization clinics. The propensity for these clinics is not explicitly known. Nonetheless, it is our conjecture that acquiring the vaccine without the need to visit a physician offers a safe sense of anonymity and privacy, as well as, avoidance of questions regarding sexual orientation.

Due to the relative newness of the Gardasil™ vaccine, there is limited published literature on post-marketing usage patterns and adherence rates among various populations. Three academic centers have reported similar low overall adherence rates in 9–26 year-old females, i.e. the University of Cincinnati (28%), University of Maryland (29%), and University of Michigan (19–26 year-olds) (10%) [17–19]. Higher adherence rates (43%) were demonstrated in 9–26 year-olds belonging to a California managed care organization and residents of North Carolina (55%) [25,26]. The highest (64%) was among 12 year-olds in La Spezia, Italy after an HPV vaccination campaign [27]. A possible explanation for the greater adherence rates among pre-adolescents as replicated in our study is the extent of parental education and depth of child-parent involvement. The limited national statistics identified in the literature were found in the CDC's National Immunization Survey-Teen as cited in the Introduction [15,16]. As for global statistics, HPV vaccine adherence rates are unknown. In the "WHO vaccine-preventable diseases: 2010 global summary" issued by the World Health Organization which contains statistical data of immunization programs from 193 countries, HPV vaccination has been incorporated in the immunization schedules of 29 Member States as of 2009 [28]. Howbeit, immunization coverage levels calculated as a percentage of target population vaccinated and the number of doses completed has not been reported for HPV vaccination. This is in contradistinction to HepB3 (3rd dose hepatitis B vaccine) and Hib3 (3rd dose Haemophilius influenza type b vaccine) which are examples of tracked immunizations by WHO [29]. Furthermore, if we measured our findings against the U.S. Department of Health and Human Services *Healthy People 2010* [15,29] benchmark set at 90% vaccine coverage of all immunizations and 90% coverage of ≥3 doses HepB (another multi-dose vaccine), our qHPV 3-dose adherence rate would be significantly under target.

In health services research, outcomes of evaluation are often defined in terms of efficacy, effectiveness, or efficiency. The term effectiveness is a measure of outcome in a "real-world" situation or post-marketing setting where the ideal, controlled conditions of a clinical trial are removed. The results gleaned from this study revealed the effectiveness or lack thereof of a vaccine program. Specifically, we discovered low overall adherence (32%) by using the 3-dose completion rate as the index of effectiveness (Supplementary Fig. S2). If a vaccine program is used ineffectively, its efficacy is compromised and its efficiency (benefit-cost ratio) diminished. The eventual impact would be twofold, that is, a detriment to population health and health expenditure.

The strength of this study lies in the large sample studied which is capable of generating population statistics and trends. This was made possible with the use of AHLTA which is a repository of outpatient medical records of all U.S. military beneficiaries (~9.4 million) [30]. This study captured almost 7000 military beneficiaries from the San

Diego metropolitan area who visited numerous clinics at various locations. Since AHLTA is the common digital repository, those who received their inoculations at different sites on different dates were captured and recorded. It is possible that some patients may have received or completed the vaccine series in the civilian sector resulting in loss of data. Examples of civilian sources of qHPV vaccination include private-practice physicians, university hospitals or clinics, and county health clinics. We believe this subset is small due to the difference in out-of-pocket expense, i.e. $125/dose in civilian versus $0 in the Military Healthcare System (MHS). The monetary incentive leans toward staying within the MHS which lends supports to the completeness of our data and validity of results.

Cross-sectional studies, like other types of observational research, are susceptible to errors due to chance or bias. We acknowledge that the current study has limitations. First, the potential for selection bias must be considered. The study population was derived from a large naval medical center in Southern California. Our results may not be representative of other branches of the military or the civilian population. To investigate this, a similar study is planned to survey the Army and Air Force beneficiaries of San Antonio Military Medical Center (SAMMC) in San Antonio, Texas. Second, this study is limited in terms of understanding the rationale behind non-adherence. The underlying cognitive, psychosocial, behavioral, and/or circumstantial reasons, as identified in adherence research, were not assessed due to the nature of the design and the use of electronic medical records as the data source. Previous studies have also examined socioeconomic reasons and insurance status as predictors of poor adherence [17–19,25]. These particular concerns may not be applicable to the military population since health care insurance is essentially universal. Instead, military unique circumstances must be explored to understand the disincentives for vaccine completion. We surmise that inconvenience, time-constraints, side effects (pain at injection site), relocation, and deployments all have an impact on vaccine non-adherence. In particular, U.S. deployment statistics are staggering with current and unforeseen long-term social, emotional, and behavioral effects on the service member, their children and families [31]. Since September 2001, over 2 million U.S. service members have deployed to Afghanistan or Iraq and 800,000 have deployed at least twice [31]. Decidedly, further investigation is urgently needed to answer the question “what causes non-adherence” in effort to design meaningful interventions.

In conclusion, this study has provided insight into the real-world suboptimal use of Gardasil™ HPV vaccine. Establishing an HPV vaccine registry and monitoring program at our medical centers and clinics may improve adherence rates which is paramount to achieving optimal benefit from the quadrivalent vaccine. At the current state, the true efficacy of HPV vaccination among the populace remains uncertain.

Conflict of interest

The authors have no conflicts of interest to declare.

Financial disclosure

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.ygyno.2011.07.094.

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