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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 $2 \pm 1$ month and month $6 \pm 2$ 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 $\chi^2$ 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%)), ($\chi^2$, $P<0.001$). 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%), ($\chi^2$, $P<0.001$)). Beneficiary status was also found to be associated with adherence. The 3-dose completion rates declined significantly ($\chi^2$, $P<0.001$) 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), ($\chi^2$, $P<0.001$). Among the 3 demographic categories, the groups that demonstrated the highest 2nd and 3rd dose adherence rates ($\chi^2$, $P<0.001$) were age group