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Human papillomavirus vaccine series completion in boys before and after recommendation for routine immunization

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ABSTRACT

Background: Although the incidence of HPV-attributable cancers in males is rapidly increasing, HPV vaccine uptake in males remains poor. While quadrivalent human papillomavirus vaccine (4vHPV) series initiation in males increased following the Advisory Committee Immunization Practices (ACIP) male routine use recommendation, its impact on 4vHPV series completion in males at ACIP-recommended intervals has not been evaluated in large male cohorts. We examined trends and correlates of 4vHPV completion since licensure in males in a large cohort of insured boys before and after the ACIP routine use recommendation.

Methods: We grouped data from electronic medical records of males aged 9–17 years from Kaiser Permanente Southern California health plan who initiated 4vHPV into 3 cohorts by 4vHPV initiation date: licensure and ACIP permissive use: 2009–2010; addition of anal cancer indication: 2010–2011; ACIP routine use: 2011–2013. We estimated adjusted hazard ratios (AHRs) between patient and provider characteristics and vaccination using Marginal Cox proportional hazards models.

Results: Of 80,800 boys initiating 4vHPV, 24.3% completed the series within 12 months with minimal differences across cohorts. Completion decreased with increasing age at initiation (13–17 vs. 11–12 year olds: AHR = 0.85; 95% confidence interval [CI] = 0.80, 0.89) and was greater among patients with a primary care provider (AHR = 1.28, 95%CI = 1.17, 1.41), influenza vaccine recipients (AHR = 1.50, 95% CI = 1.43, 1.57), and Asian/Pacific Islanders (AHR = 1.07, 95% CI = 1.00, 1.15), and lower among non-Hispanic Blacks (AHR = 0.72, 95% CI = 0.65, 0.80) and Hispanics (AHR = 0.86, 95% CI = 0.81, 0.90) compared to non-Hispanic Whites.

Conclusions: Despite the ACIP routine use recommendation in males, 4vHPV series completion remained low. 4vHPV initiation at 11–12 years and identification of a provider responsible for the adolescents' health care may increase 4vHPV series completion. Given the rapidly increasing incidence of HPV-related cancers in males, it is important to identify measures to increase HPV vaccine series completion, particularly among non-Hispanic Black and Hispanic males.

1. Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States. An estimated 14 million persons are newly-infected with HPV each year in the US with nearly half occurring in adolescents and young adults [1]. While most HPV infections are self-limited, persistent HPV infections cause over 30,000 cancers in the US annually [2].

Three HPV vaccines licensed in the US protect against infection with HPV types 16 and 18 which cause over 60% of cervical and oropharyngeal HPV-related cancers [3,4]. In addition, quadrivalent (4vHPV) and nonavalent (9vHPV) HPV vaccines protect against HPV types 6 and 11, which cause 90% of genital warts, and 9vHPV protects against five additional oncogenic HPV serotypes [4,5]. In 2006 the Advisory Committee on Immunization Practices (ACIP) recommended routine vaccination of females 11–12 years of age and catch-up vaccination of females 13–26 years of age with a ser-

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ies of 3 doses of 4vHPV given at 0, 1–2, and 6 months after initiation [4]. However, 4vHPV was not licensed for use in males by the Food and Drug Administration (FDA) until 2009 [6] and the ACIP recommendation for permissive use of 4vHPV for the prevention of genital warts in males 9–26 years of age was not published until 2010 [7]. Prevention of anal cancer was added as an FDA indication for 4vHPV in 2010 [8]. Routine 4vHPV vaccination of males 11–12 years of age with catch-up vaccination of males 13–21 years of age was recommended by the ACIP in 2011 [9].

Given the high efficacy of 4vHPV among males [10] and suboptimal vaccination coverage among females [11], HPV vaccination of males is likely to benefit females through herd immunity. Furthermore, HPV vaccination will likely play an important role in stemming the increasing incidence of HPV-related oropharyngeal cancers in males that is likely to exceed that of cervical cancer in the US by 2020 [12]. While the HPV-attributable incidence of oropharyngeal cancers in the United States was estimated to have increased by 255% between 1988 and 2004 (0.8 and 2.6 per 100,000, respectively), it is estimated to have increased further from 3.9 to 5.5 per 100,000 in males between 2004–2008 and 2008–2012 [2,12,13].

Although data from the National Immunization Survey-Teen (NIS-Teen) showed that initiation of 4vHPV in teen boys increased since the 2011 ACIP recommendation to routinely vaccinate males with 4vHPV, only 28.1% of male teens received 3 or more doses by 2015 [11]. Few studies have evaluated predictors of 4vHPV series completion in males. Available studies analyzed small male samples or utilized NIS-Teen data which does not assess uptake among 11–12 year olds for whom routine HPV vaccination is recommended or assess dosing intervals and timely completion [14–17]. In this study we examined rates and correlates of timely 4vHPV series completion within 12 months in a large sample of insured adolescent males 9–17 years of age during the periods before and after the ACIP routine 4vHPV recommendation for males.

2. Methods

This observational retrospective cohort study was conducted at Kaiser Permanente Southern California (KPSC), an integrated health care system with over 4 million members representative of the diverse background of Southern California residents [18]. All members of KPSC were fully covered for the cost of ACIP-recommended vaccines and could receive 4vHPV at any clinic visit, including no-cost nurse visits.

We identified 3 open cohorts of boys aged 9–17 years who initiated 4vHPV series during 3 observation intervals corresponding to FDA licensure for protection against genital warts in males and ACIP permissive use in males (October 21, 2009–December 21, 2010), additional anal cancer indication (December 22, 2010–October 24, 2011), and the ACIP routine use recommendation in males (October 25, 2011–May 31, 2013), detailed previously [19]. In a supplemental analysis, we identified males who initiated the series after the ACIP permissive use but prior to publication of the ACIP routine use recommendation in males (May 28, 2010–December 23, 2011) and those that initiated after the ACIP routine use recommendation publication (December 24, 2011–May 31, 2013).

We identified males who had initiated the 4vHPV series (i.e., received their first dose) during each observation period and the status of 4vHPV series completion through KPSC electronic medical records (EMR). KPSC EMR contained health plan members' immunization history, including all vaccines administered in KPSC facilities and elsewhere before and during the enrollment period. If the member or their caregiver reported receiving a vaccination outside of KPSC, a nurse requested documents to ascertain the vaccine name, dose, and vaccination date, and entered this information into the EMR. We followed males aged 9–17 years at initiation of the first dose of the 4vHPV series during the observation period of each cohort until completion of the 4vHPV series, membership disenrollment, or one year after the end of the third observation interval (May 31, 2014), whichever came first. The main outcome of the study was completion of the 3-dose series within 12 months of initiation. Among those completing the 3-dose series within 12 months, we also assessed whether the doses were given in accordance with the minimum ACIP intervals: at least 28 days between doses 1 and 2, at least 84 days between doses 2 and 3, and at least 168 days between doses 1 and 3 [4].

We ascertained socio-demographic characteristics, assigned primary care provider (PCP), having a sister aged 9–17 years of age and healthcare utilization of boys who initiated 4vHPV vaccination through membership files. To mirror the recommended age groups for routine vaccination, we categorized boys into 3 age groups at initiation: 9–10 years, 11–12 years and 13–17 years. We categorized boys as having Hispanic race/ethnicity if Hispanic was reported as their ethnicity. Preferred spoken language was that reported in the EMR by caregivers. To obtain neighborhood education and income levels as a proxy for family socioeconomic status, we mapped the home address to US census block. We also used enrollment in Medicaid as a proxy indicator for low SES.

We defined health care utilization as the number of outpatient and emergency department visits and hospitalizations during the year before initiation. Since vaccine recommendations of PCPs play an important role in parents' decisions to vaccinate their children [20], we examined potential associations between 4vHPV completion with whether a boy had an assigned PCP and PCP specialty at initiation. As influenza vaccine uptake might indicate vaccine acceptance, we ascertained influenza vaccination up to one year before 4vHPV initiation.

Discrete categorical cohort characteristics were compared between boys who completed the 3-dose series and those who did not using the Pearson chi-square test. The student *t*-test was used to test differences in normally distributed continuous variables, while the Wilcoxon rank sum test was used to compare ordinal variables.

Marginal Cox proportional hazards models were used to assess the relationship between clinical and demographic characteristics and HPV series completion within 12 months among participants with at least one year of membership prior to initiation of 4vHPV. These models accounted for cluster effects within medical centers and allowed for varying follow-up times within the cohort. Robust sandwich covariance matrix estimates were used to account for the intra-cluster dependence within medical centers. The proportional hazards assumptions were verified using Kaplan-Meier curves and testing for time by variable interaction terms (age, race/ethnicity, language, education, income, Medicaid, PCP category and female sibling). All variables significant at the 0.05 level in a bivariate model were candidates for the fully adjusted models. A language by race/ethnicity interaction term was tested but non-significant in all cases. Hazard ratios (HR) and 95% confidence intervals (CI) were reported.

All analyses were performed using SAS Enterprise Guide 5.1 (SAS Institute, Inc.).

The KPSC Institutional Review Board approved the study protocol.

3. Results

We initially performed separate bivariate and multivariable analyses of the 3 cohorts of boys aged 9–17 years who initiated