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HPV vaccination series completion and co-vaccination: Pairing vaccines may matter for adolescents

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Abstract

Very little is known about the effect of concurrent co-vaccination on HPV series completion. This study utilized a retrospective review of a Clinical Data Repository to assess whether concurrent vaccination had an impact on HPV vaccination series completion, and whether there were differences based on age. 3371 patients who received the HPV vaccine at a single academic medical center between the years 2009-2013 were included in this analysis. The adjusted odds ratio (aOR) for effect of concurrent vaccination on series completion for the age group 9-18 was 1.32 (95% CI 1.09,1.60). Although not statistically significant, the aOR for effect of concurrent vaccination on completion changed direction for the 19-25 age group and was 0.44 (95% CI 0.17, 1.12). This study provides preliminary evidence that pairing the HPV vaccine with one or more co-vaccines may yield a higher HPV vaccination completion rate among adolescents age 9-18.

Keywords

HPV vaccine; adolescent; young adult; co-vaccination; compliance

Introduction

The human papillomavirus (HPV) infection is an established risk factor for the development of several types of cancer, including cervical, vulvar, vaginal, oropharyngeal, penile, and anal cancer with prevalence peaking in young adulthood[1,2]. The quadrivalent HPV vaccine, a three series vaccination, was licensed for use in females in 2006 and males in 2009 to protect against diseases caused by HPV subtypes 6, 11, 16 and 18, and up until 2014

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was the most commonly administered HPV vaccine [3]. The Advisory Committee on Immunization Practices (ACIP) recommends vaccination of girls and boys age 11-12 (acceptable range of vaccination 9-26 for females; 9-21 for all males and up to 26 for men who have sex with men or immunocompromised males)[1].

Despite the recommendations, HPV vaccination initiation and series completion rates have been dramatically lagging behind anticipated vaccination rates for both females and males. In 2012 in the United States, 53.8% of females obtained at least the first vaccine but only 33.4% obtained all three[4]. Even though vaccinating males is a newer recommendation, in 2012 the initiation percentage was 20.8% for males, with only 6.8% completing the three-series for full coverage[4].

Globally, pairing non-vaccine public health interventions along with the HPV vaccination to increase vaccine initiation and completion has yielded inconsistent results[5]. The purpose of this study was to determine if co-vaccination of another vaccine along with the HPV vaccine predicts completion of the HPV three-series among patients who received at least one dose in an academic medical center in Virginia, USA. We also wanted to determine if there was a difference in completion with co-vaccination by age (comparing adolescents versus young adults).

Methods

Sample selection

This retrospective study received Institutional Review Board exemption prior to study initiation. The University of Virginia's Clinical Data Repository (CDR) was used for subject identification based on a single query. Participants were identified using the procedure codes for having received at least one HPV vaccination from 2009-2013. Participants from years 2009 and 2013 were followed back and forward in time respectively to ensure accurate data of completion of the series was obtained. Other variables collected included: number of HPV doses received (completion of three series variable created), age, gender, payer (private insurance, Medicaid or self-pay), race (white vs. non-white), region (county), and co-vaccination at the time of first HPV vaccine administration (yes/no).

Analysis

Patients were sampled from the region shown in Figure 1. In order to proceed with the analysis using complete data, 3 patients who lacked completion data were eliminated, as were 5 patients who lived extraneous to the region, and 3 patients without insurance data, for a total of 3,371 patients with complete information. Descriptive statistics were calculated to describe all variables.

Bivariate and multivariate analysis by age and category strata were conducted using logistic regressions. For the multivariate analysis, a random effects logistic regression was conducted using the Stata version 13 procedure 'meqrlogit'[6], with the probability of completion treated as the dependent variable, concurrent vaccination and the covariates included as the predictor variables, and a random effect for each county in the region added to the linear predictor in order to control for unseen county-level contextual effects. In

addition to displaying and estimating odds ratios, we also calculated marginally standardized probabilities of completion for each predictor so that risk differences could be assessed on the probability scale [7]. These probabilities were calculated by averaging the model based predicted probabilities over the sample of observations while setting the predictor's value at the same level for each observation.

Logistic regression parameters for each covariate by age strata (adolescents age 9-18 versus young adults age 19-25) were compared using statistical tests of interaction with age category and set to equality if the null hypothesis of equality was not rejected. In order to examine potential effect modification for the effect of concurrent vaccination on completion, the statistical interactions between concurrent vaccination and each covariate in the model were individually tested.

Results

Overall, 3371 patients were included in this analysis and sample characteristics are described in Table 1. Only 25% of this sample completed the three-series HPV vaccine. The majority of the sample was female, white, had private insurance, and received a concurrent vaccination along with their first dose of the HPV vaccine.

Results for the bivariate and multivariate models can be found in Table 2. The adjusted odds ratio (aOR) for effect of concurrent vaccination on completion for the age group 9-18 was 1.32 (95% CI 1.09,1.60) with 34% completion rate projected in a representative sample of cases with concurrent vaccination compared to 24% for cases without. Although not statistically significant, the aOR for effect of concurrent vaccination on completion changed direction for the 19-25 age group and was 0.44 (95% CI 0.17, 1.12), with rates of 10% versus 13% respectively. Additionally, all of the aOR for the variable "starting year" were statistically significant, with greater likelihood of completion of the three series most distant year, with each subsequent year yielding less of a marginal probability of percent completion.

A statistical interaction was significant at $\alpha = .05$ ($p = 0.024$), suggesting the effects are significantly different between age groups. Interaction tests for concurrent vaccination with other covariates were not significant at an α of .05. Furthermore, the likelihood ratio test testing for the concurrent vaccination effect heterogeneity by region had a p-value of 0.9867. As a result, the random intercept model was selected as the final model in Table 2 and the effects of concurrent vaccination were treated as global effects across the entire study region.

A trend that warrants further study is the steady decrease of HPV series completion from 2009 to 2013. The Wald test of time trend (equality of parameter estimates in the model from Table 2) was significant with $p < .0001$. All enrollees during 2009 (100%) and most during 2010 (98%) were women, with progressive representation of males from 2011 to 2013 (22%, 47% and 45%). From 2011 to 2013, a Wald test of interaction in a logistic regression model predicting completion with only gender, year, and interaction term was significant with $p < .0001$, suggesting that trend varies by gender. Completion rates for males

from 2011-2013 were 23%, 24%, 16%. Completion rates for females were 29%, 25%, 17%. Results suggest a greater rate of decrease of females than males during this time period, though this may be attributable to increased discrepancy in rates in 2011 only.

Discussion

This study provides preliminary evidence that pairing the HPV vaccine with one or more co-vaccines may yield a higher percent completion among adolescents age 9-18. Although not statistically significant, the trend reverses among young adults, indicating the relationship between HPV vaccination and co-vaccination may not be relevant for those who are 19-25. Findings from this descriptive pilot study are hypothesis-generating because it highlights the differences in effective intervention pairing among these two age groups and calls for further study.

One limitation of this study was the inability to collect data on what co-vaccination was given, only that a co-vaccination was received. In the adolescent age group the co-vaccines are likely to include: tetanus, diphtheria, pertussis (Tdap), meningococcal (MC4) (both index dose and booster) and influenza vaccine; whereas the co-vaccine in the young adult group is more likely to be the influenza vaccine unless catch-up vaccination is warranted[4]. Because Tdap and MC4 have higher levels of acceptability and initiation among adolescents[4], these specific vaccines may be driving much of the effect, but further study is needed to make that determination.

Providers who make strong recommendations about vaccines are likely to have higher uptake and completion rates [2] and the Tdap, MC4, and HPV are often presented at the 11-year old well check-up visit as a concurrent bundle of scheduled vaccinations. Another limitation of this study is that parents and adolescents who are more likely to vaccinate with the other recommended vaccines may be more likely to complete the HPV 3-series due to other factors influencing vaccine acceptability, so we cannot eliminate the potential confounding from this demonstrated effect of co-vaccination and series completion among adolescents.

Finally, this sample was derived from a single academic medical center with a variety of potential settings that adolescents and young adults could have received the HPV vaccination (pediatric primary care, pediatric specialty care, family medicine, obstetrics and gynecology, the Teen Health Center, Student Health, etc). There may be certain practice settings that have extremely high completion rates due to their approach (such as clinic-provided reminders), but these setting-specific differences in completion rates were not able to be abstracted from the secondary data. Additionally, this medical center has a large rural catchment area, so the findings may not be generalizable to other care settings.

One hypothesis addressing the steady decrease of HPV series completion is that there may have been an early, more systematic adoption of the vaccine in the years directly following legislation mandating that 11-12 year old girls in the Commonwealth of Virginia be vaccinated with the HPV vaccine (legislation signed into law in 2007)[8]. However, the widely criticized broad opt-out options for young women, plus the failed attempts to have

males included in the mandatory legislation in Virginia[8] may have mitigated the long-term anticipated impact of the legislation.

More research is needed into system-based and public health interventions that can lead to higher completion of the three-series HPV vaccine. Much of the work to date has focused on individual and provider-level barriers to initiation and completion, and further study is needed to delineate interventions (e.g. co-vaccination) and process-variables from a systems-perspective that can lead to higher coverage HPV vaccine coverage among adolescents and young adults.

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Figure 1. Study Sample Region with Patient Counts

Table 1
Participant characteristics among those who initiated HPV vaccination at an academic medical center (n = 3371)

Variable	Age 9-18		Age 19-25		Overall	
	N	% Complete	N	% Complete	N (%)	% Complete
Completion						
Yes	821	-	35	-	856 (25)	-
No	2,195		320		2,515 (75)	
Concurrent vaccination						
Yes	2,066	29	113	5	2,180 (65)	28
No	949	22	242	12	1,191 (35)	20
Gender						
Male	1,040	20	75	8	1,115 (33)	20
Female	1,976	31	280	10	2,256 (67)	28
Insurance						
Private	2,164	27	311	9	2,475 (73)	25
Medicaid	724	27	15	13	739 (22)	27
Self-pay	128	27	29	14	157 (5)	25
Race						
Non-white	593	20	95	3	688 (20)	27
White	2,423	29	260	12	2,683 (80)	18
Start Year						
2009	338	47	79	16	417 (12)	41
2010	268	45	34	15	302 (9)	41
2011	430	31	51	4	481 (14)	28
2012	714	26	81	12	795 (24)	25
2013	1,266	18	110	5	1,376 (41)	17
Overall	3,016	27	355	10	3,371	25

Table 2
Unadjusted and Adjusted Odds Ratios (stratified by Age Group) predicting HPV Series Completion

Variable	Unadjusted OR with 95% CI	Adjusted OR with 95% CI 9-18 age group	Adjusted OR with 95% CI 19-25 age group	Marginally Standardized Probabilities (% Completers)
Age 9-18				
Concurrent vaccination				
Yes	1.44(1.20,1.72)	1.32 (1.09,1.60)	-	34
No	1.0 REF	1.0 REF		24
Age 19-25				
Concurrent vaccination				
Yes	0.41(0.17,1.02)	-	0.44 (0.17,1.12)	10
No	1.0 REF		1.0 REF	13
Age 9-25				
Gender				
Female	1.61 (1.35,1.92)	0.97 (0.78,1.19)	0.97 (0.78,1.19)	25
Male	1.0 REF	REF	1.0 REF	26
Insurance				
Private	1.01 (0.70,1.47)	2.01(1.34,3.03)	2.01(1.34,3.03)	27
Medicaid	1.11 (0.75,1.65)	1.51(0.98,2.33)	1.51(0.98,2.33)	22
Self-pay	1.0 REF	1.0 REF	1.0 REF	17
Race				
Non-white	0.59(0.47,0.72)	0.68 (0.54,0.85)	0.68 (0.54,0.85)	20
White	1.0 REF	1.0 REF	1.0 REF	27
Starting Year				
2009	3.54(2.78,4.50)	4.49 (3.36,6.01)	4.49 (3.36,6.01)	43
2010	3.56(2.72,4.66)	3.48 (2.56,4.73)	3.48 (2.56,4.73)	37
2011	1.97(1.54,2.51)	2.31 (1.76,3.04)	2.31 (1.76,3.04)	29
2012	1.65(1.33,2.04)	1.98 (1.56,2.51)	1.98 (1.56,2.51)	26
2013	1.0 REF	1.0 REF	1.0 REF	16

Note: Adjusted OR's were derived from the random effects logistic regression model, where concurrent vaccination parameter estimates and odds ratios were allowed to vary by age group. Other covariate parameters were tested for equality using statistical interaction with age group and pooled if test of interaction was not significant.