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Operationalizing Outcome Measures of HPV Vaccination among Adolescents

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Abstract

Objectives: When examining vaccination coverage, researchers must make decisions about how to define outcome measures based on many factors, including the timing of doses. Different operationalizations of the same outcome can often lead to different findings and can affect the ability to make comparisons across studies. This methodological paper aimed to illustrate the implications of two options for operationalizing HPV vaccination based on timing: initiation of the first dose at any age versus prior to the 13th birthday (on-time).

Study Design: Cross-sectional observational design

Methods: The 2014 National Immunization Survey for Teens (NIS-Teen, N=16,439 adolescents ages 13-17) was analyzed using multivariate logistic regression for each outcome measure and effect modification by gender.

Results: Age was positively associated with initiation at any age, but negatively associated with on-time initiation. Gender modified the effect of race/ethnicity for both measures of initiation, but the pattern across groups was different for the two outcomes. Gender modified the effect of provider recommendation for initiation at any age, while gender modified the effects of age and region for on-time initiation.

Conclusion: Decisions of how to operationalize outcomes of HPV vaccine initiation among adolescents can lead to different conclusions about the role of age and gender differences for several predictive variables. In order to inform the development of public health efforts that promote on-time HPV vaccination among male and female adolescents, researchers should consider the importance of dose timing when operationalizing outcome measures. We recommend including on-time receipt of the HPV vaccine as an outcome measure.

Keywords: Human papillomavirus vaccine, Immunization schedule, Adolescent, Gender

Operationalization refers to the process of defining how a concept or phenomenon will be measured, which forces the researcher to make decisions about specific parameters for each variable. In the case of vaccination, choices must be made regarding timing, number of doses, or denominator limitations.[1] Different operationalizations of the same concept can often lead to different findings and can affect the ability to make comparisons across studies.[1]

Human papillomavirus (HPV) vaccination has been recommended in the U.S. for female adolescents since 2006 and males since 2011.[2] In the U.S., HPV vaccine is primarily administered in primary care or public health department settings, with limited access in other settings such as schools or pharmacies. Through the federal Vaccines for Children program, children under age 18 can receive the vaccine at no cost if they are publicly insured under Medicaid, underinsured (i.e., coverage does not include vaccines), uninsured, or American Indian or Alaskan Native. However, uptake of the vaccine has been slow, particularly among males.[3]

HPV vaccination is recommended at 11-12 years of age, with late vaccination available through age 26.[2] Under age 13, immune response is highest and virus exposure is low.[4]. However, most studies assessing determinants of HPV vaccine coverage among adolescents in the U.S. have operationalized HPV vaccination based on doses received at any age prior to 18.[3,5,6] Very few studies have examined determinants of *on-time* vaccination prior to age 13, and they primarily used data on females only.[7–9] The decision of how to operationalize the timing of HPV vaccination, i.e., any age versus on-time vaccination, could potentially lead to different

conclusions about patterns of vaccination coverage and opportunities for interventions to promote adherence with the recommended immunization schedule. This methodological paper aimed to illustrate the implications of operationalizing the outcome of HPV vaccination at any age versus on time.

This study used a cross-sectional observational design. The National Immunization Survey for Teens (NIS-Teen) is a nationally-representative public health survey of a stratified, probability sample of households in the U.S.[3] NIS-Teen consists of a random-digit-dialed household survey of parents of adolescents aged 13–17 years and verification of vaccination histories from healthcare providers.[10] Details of the NIS-Teen methodology, response rate, and sample characteristics have been published elsewhere.[3] The NIS-Teen documentation advises to use the subset of adolescents with provider-verified data to generate estimates of vaccine coverage, due to the low reliability of parent-reported vaccination for adolescents.[10] The 2014 NIS-Teen public use data file contained 38,703 adolescents. First 17,646 adolescents (45.6%) were excluded from the analysis because provider-verified immunization data were not available, then 2,142 (5.5%) were excluded because their self-reported race/ethnicity was Asian or other, given the small numbers and heterogeneity of this group. Finally, 2,476 (6.4%) cases with missing data on the variables included in the analyses were excluded. The final analytical sample size was 16,439 adolescents.

The following two alternatives for operationalizing HPV vaccination were examined:

1) *Initiation at any age:* Received one or more doses HPV vaccine at any age (1=Yes, 0=No)

2) *On-time initiation:* Received one or more doses HPV vaccine before the 13th birthday (1=Yes, 0=No)

The independent variables were gender (female, male), age (13-14 years, 15-17 years), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic of any race), family poverty (above federal poverty line, below federal poverty line), geographic region (South, Northeast, Midwest, West), having received a healthcare provider recommendation for HPV vaccine (no, yes), health insurance (insured, uninsured), doctor visits in the past year (0 or 1, more than 1), parent's education (less than college degree, college degree or higher), and parent's marital status (unmarried, married). Data were analyzed with SAS version 9.4 using multivariate logistic regression procedures that accounted for the complex sampling design. First the base models were estimated for each outcome variable, including all of the independent variables listed above. Next, an interaction term with gender and each of the nine independent variables was added to the base model one at a time, in nine separate models for each outcome variable. Two-tailed statistical significance level was set at alpha < 0.05.

The sample was comprised of 52% males and 48% females (data not shown). Approximately 60% of the adolescents were 15-17 years old at the time of the survey. The racial/ethnic composition was 61% non-Hispanic white, 15% non-Hispanic black, and 24% Hispanic of any race. A larger portion of the adolescents (39%) were from the South versus other regions. The percentage of parents reporting that they had received a healthcare provider recommendation for HPV vaccine was 54.2% for males and 75.7% for females ($P<0.0001$). Among all 13-17 year-olds, 43.1% of males and 60.7% of females received at least one dose of HPV vaccine at *any*

age, while 15.6% of males and 38.2% of females received the first dose *on time* before the 13th birthday.

In the base multivariate logistic regression model for HPV vaccine initiation *at any age* (Table 1), the odds of ever receiving at least one dose of HPV vaccine was lower for teens who were male (adjusted odds Ratio [AOR]=0.68; 95% confidence interval [CI], 0.60-0.78), but higher for those who were 15-17 years old (AOR=1.32; 95% CI, 1.15-1.52), Hispanic (AOR=1.75; 95% CI, 1.42-2.15), black (AOR=1.29; 95% CI, 1.04-1.59), poor (AOR=1.58; 95% CI, 1.28-1.94), living in the West (AOR=1.31; 95% CI, 1.06-1.63), and received a provider recommendation (AOR=6.45; 95% CI, 5.50-7.55). In the stratified models, two variables had significantly different effects by gender, race/ethnicity (higher odds for Hispanic males and black females, *P*=0.004) and provider recommendation (stronger positive effect for males, *P*=0.003).

Next, we replicated the same models for HPV vaccine initiation *prior to age 13* (Table 1). In the base model, only the effect of age differed from the first model, with older adolescents having lower odds of on-time vaccination (AOR=0.37; 95% CI, 0.32-0.43). In the stratified models, the effect modification by gender was significant for age (stronger negative effect for males, *P*<0.001), race/ethnicity (higher odds for Hispanic males and black males, *P*=0.01), and region (lower odds for males in the Northeast and higher odds for males in the West, *P*=0.006). In contrast to the first model, provider recommendation did not differ significantly by gender (*P*=0.08).

In summary, comparing the results of the two different operationalizations of HPV vaccine initiation, we found that age was positively associated with initiation at any age, but negatively

associated with on-time initiation. Gender modified the effect of race/ethnicity for both measures of initiation, but the pattern varied for black adolescents, with any age initiation higher for black females but on-time initiation higher for black males. Gender modified the effect of provider recommendation for initiation at any age, while gender modified the effects of age and region for on-time initiation.

Annual NIS-Teen reports have consistently shown higher HPV vaccine initiation at any age for females, older teens, blacks, Hispanics, and teens living in poverty, but inconsistent regional patterns.[3] However, these reports have not applied multivariate analyses to estimate the independent effect of each variable while controlling for potential cofounders. Results of our multivariate analyses of HPV vaccination at any age were consistent with NIS-Teen reports and previous studies,[5,6] showing higher initiation among females, older teens, blacks, Hispanics, and teens living in poverty, along with higher initiation in the Western region, after adjusting for other variables. However, changing the outcome measure to on-time initiation impacted the effect of age, flipping it from a positive to negative association, with younger adolescents more likely to have received the first dose before age 13.

Previous studies have not examined effect modification by gender for determinants of on-time HPV vaccine initiation. Our analyses demonstrated that the presence or absence of effect modification by gender differed across the two outcome measures for age, race/ethnicity, region, and provider recommendation. Consistent with previous studies,[5,6,8] the strongest determinant overall was provider recommendation, with six-fold higher odds of initiation at any age and three-fold higher odds of initiation before 13. The effect of provider recommendation on

initiation at any age was stronger for males than females, but a significant effect modification by gender was not observed for on-time initiation for this variable.

A limitation of the current study is the potential for confounding effects of unmeasured covariates, such as vaccine attitudes. Another limitation is the potential bias introduced by excluding cases without provider-verified immunizations or other missing data.

In conclusion, this methodological analysis illustrated the importance of considering the timing of vaccination when making decisions about how to operationalize HPV vaccination outcome measures. Defining the outcome as vaccination at *any age* versus *on-time* could potentially lead to different conclusions about patterns of HPV vaccination coverage and the identification of intervention opportunities to promote adherence with the recommended immunization schedule. These analyses could also be replicated to compare any age and on-time completion of the multi-dose HPV vaccine series and to compare with samples from other countries. Given these differences and the superior immune response to HPV vaccine before age 13, we recommend that researchers include *on-time* vaccination as one of the outcome measures, if not the *primary* outcome measure, in future observational and intervention studies. As more studies include on-time HPV vaccination as an outcome, comparisons of findings for this outcome can be made across studies.

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Table 1: Determinants of HPV Vaccine Initiation at Any Age and HPV Vaccine Initiation Prior to Age 13, among 13-17 Year Old Adolescents in the U.S., Stratified by Gender

	Base Model (No Interactions) Adjusted OR[b] (95% C.I)	Gender Stratification[a]		
		Male Adjusted OR[b] (95% C.I)	Female Adjusted OR[b] (95% C.I)	*P*-Value for Interaction
HPV Vaccine Initiation at Any Age				
Gender				
Female (Ref)	1.00	--	--	--
Male	0.68 (0.60-0.78)			
Teen Age				
13-14 years (Ref)	1.00	1.00	1.00	0.051
15-17 years	1.32 (1.15-1.52)	1.16 (0.96-1.40)	1.52 (1.25-1.85)	
Teen Race/Ethnicity				
Non-Hispanic White (Ref)	1.00	1.00	1.00	0.004
Non-Hispanic Black	1.29 (1.04-1.59)	1.19 (0.88-1.59)	1.38 (1.03-1.86)	
Hispanic (any race)	1.75 (1.42-2.15)	2.35 (1.81-3.04)	1.29 (0.97-1.73)	
Family Poverty				
Above poverty level (Ref)	1.00	1.00	1.00	0.71
Below poverty level	1.58 (1.28-1.94)	1.63 (1.27-2.09)	1.52 (1.13-2.05)	
Region of Country				
South (Ref)	1.00	1.00	1.00	0.31
Northeast	1.14 (0.96-1.34)	1.16 (0.93-1.46)	1.11 (0.87-1.42)	
Midwest	1.04 (0.90-1.21)	0.95 (0.78-1.17)	1.14 (0.92-1.41)	
West	1.31 (1.06-1.63)	1.44 (1.08-1.91)	1.19 (0.86-1.65)	
Provider Recommendation				
No (Ref)	1.00	1.00	1.00	0.003
Yes	6.45 (5.50-7.55)	7.93 (6.45-9.76)	4.98 (3.93-6.32)	
HPV Vaccine Initiation Prior to Age 13				
Gender				
Female (Ref)	1.00	--	--	--
Male	0.33 (0.28-0.38)			
Teen Age				
13-14 years (Ref)	1.00	1.00	1.00	<0.001
15-17 years	0.37 (0.32-0.43)	0.14 (0.11-0.19)	0.62 (0.52-0.75)	
Teen Race/Ethnicity				
Non-Hispanic White (Ref)	1.00	1.00	1.00	0.01
Non-Hispanic Black	1.32 (1.07-1.64)	1.63 (1.17-2.26)	1.18 (0.91-1.53)	
Hispanic (any race)	1.79 (1.45-2.20)	2.52 (1.85-3.43)	1.42 (1.09-1.85)	
Family Poverty				
Above poverty level (Ref)	1.00	1.00	1.00	0.16
Below poverty level	1.64 (1.34-2.01)	1.91 (1.44-2.52)	1.48 (1.14-1.92)	
Region of Country				
South (Ref)	1.00	1.00	1.00	0.006
Northeast	0.84 (0.70-1.02)	0.68 (0.50-0.93)	0.95 (0.74-1.22)	
Midwest	1.09 (0.92-1.28)	0.91 (0.70-1.18)	1.19 (0.97-1.47)	
West	1.30 (1.03-1.64)	1.71 (1.21-2.42)	1.07 (0.80-1.44)	
Provider Recommendation				
No (Ref)	1.00	1.00	1.00	0.08
Yes	3.29 (2.74-3.96)	2.75 (2.09-3.62)	3.83 (3.01-4.88)	

[a]An interaction term with gender and each independent variable was added to the base model one at a time, in separate models.
[b] Odds Ratios (OR) adjusted for teen insurance coverage, teen doctor visits in past year, parent education, parent marital status, and the other variables listed in the table.