Early Initiation of HPV Vaccination and Series Completion in Early and Mid-Adolescence

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abstract

OBJECTIVES: Routine human papillomavirus (HPV) vaccination has been recommended in the United States since 2006 but rates remain suboptimal. State-based studies suggest that initiation in late childhood at ages 9 to 10 years compared with the recommended early adolescent ages of 11 to 12 years improves series completion. No study with national scope has explored the early initiation-HPV series completion relationship. This study addresses this knowledge gap and explores whether early initiation might improve series completion by increasing time to target completion age (time pathway) or by moving initiation to an earlier developmental stage (development pathway).

METHODS: Using data from the National Immunization Survey-Teen 2017-2020, a retrospective cohort of 19 575 15 to 17 year olds who initiated HPV vaccination between ages 9 and 12 years was assembled. Time pathway endpoints were series completion by ages 13 and 15 years. The development pathway endpoint was completion within 3 years of initiation.

RESULTS: Early initiators were more likely to complete by ages 13 (74.0% vs 31.1%, $P < .001$) and 15 (91.7% vs 82.7%, $P < .001$) years but less likely to complete within 3 years (82.3% vs 84.9%, $P = .007$). The association of early initiation to completion was maintained in multivariable analyses for time pathway endpoints (age 13 years adjusted odds ratios [AOR] = 6.16; 95% confidence interval [CI], 5.45–6.96, age 15 years = AOR 2.56; 95% CI, 2.14–3.14) but not the development pathway endpoint (AOR = 0.93; 95% CI, 0.80–1.07).

CONCLUSIONS: Moving routine HPV vaccination to ages 9 to 10 may improve vaccination coverage rates in early and mid-adolescence. Providers should be vigilant to patient interactions after HPV series initiation to optimize public health benefits of vaccination.

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Dr Goodman conceptualized the study, provided guidance on design and development of the analytic cohort, carried out the analyses, reviewed and interpreted results, drafted the initial manuscript, and reviewed and revised the manuscript. Dr Wang developed the analytic data set and constructed the birth cohorts from the NIS-Teen public use files, reviewed and interpreted results, and reviewed and revised the manuscript. Drs Felsher, Yao, and Chen provided guidance on conceptualization and analytic strategy, reviewed and interpreted results, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: Although routine HPV immunization has been recommended in the United States since 2006, HPV immunization rates remain suboptimal. State-based studies suggest initiation at ages 9 to 10 years increases HPV vaccination series completion but no study with national scope explores this relationship.

WHAT THIS STUDY ADDS: This National Immunization Survey (NIS)-Teen based retrospective cohort study demonstrates that early initiation at ages 9 to 10 years versus 11 to 12 years strongly predicted series completion by ages 13 and 15 years. However, early initiation was not associated with completion within 3 years of initiation.

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Human papillomavirus (HPV) is the most common sexually transmitted infection globally and contributes to more than 600 000 new cancer cases and 300 000 deaths annually.[1] In the United States, vaccination to prevent HPV infection was approved in 2006 for females and extended to males in 2010. The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination for 11- to 12-year-old children but also states that vaccination may be initiated as early as age 9 years.[2] The American Academy of Pediatrics supports routine HPV vaccination for ages 9 to 12 years and recommends immunization in the 9- to 10-year age group in communications to members.[3] Despite endorsement by both the ACIP and American Academy of Pediatrics, HPV immunization series completion rates among young people in the United States have remained stubbornly suboptimal, 58.6% among 13 to 17 year olds in 2020, well below the Healthy People 2020 target of 80%.[4] Furthermore, racial, socioeconomic, and geographic disparities in series completion have been documented.[4–6]

Increasing HPV vaccination series completion is a public health priority. Studies from Minnesota and Mississippi have suggested that initiation in early childhood at ages 9 to 10 years leads to higher HPV vaccination series completion rates compared with those who initiate in early adolescence at the recommended ages of 11 to 12 years.[7,8] To date, no study with national scope has assessed if earlier initiation is associated with improved HPV vaccination series completion nor explored mechanisms underlying such an association. Moving the age of initiation from ages 11 to 12 years to ages 9 to 10 years involves changes in both time to target age of HPV series completion and the developmental stage at which initiation occurs. Therefore, such a move could have varied impacts and effects. Understanding the pathways through which early initiation functions could help optimize series completion in early and mid-adolescence, when completion before sexual debut is more likely and maximum public health benefits would accrue.

This study addresses these gaps in the literature to assess if earlier initiation of HPV vaccination is associated with higher HPV series completion in early adolescence (by age 13 years) and mid-adolescence (by age 15 years). Furthermore, we explore 2 potential pathways through which earlier age of initiation might impact series completion. The time pathway assesses if initiation at ages 9 to 10 years compared with initiation at ages 11 to 12 years functions simply by increasing the amount of time the young person has between initiation and reaching the ages of 13 and 15 years. In contrast, the development pathway holds time from initiation to completion constant between the early and later initiation groups to explore if initiation of vaccination at ages 9 to 10 years might function by moving initiation from the early adolescent to late childhood developmental stage. We also explore if earlier initiation may modify disparities in HPV vaccination series completion.

METHODS

Sample Description

This study uses public-use data from the 2017–2020 waves of the NIS-Teen survey. NIS-Teen (https://www.cdc.gov/nchs/nis/data_files_teen.htm) is conducted by the Centers for Disease Control and Prevention and includes noninstitutionalized 13- to 17-year-old subjects from all 50 states and the District of Columbia. Although adolescents from Guam and the US Virgin Islands are included, these data are not available in the public use data files. Furthermore, data from Puerto Rico was not available in 2017 and 2018 because of hurricanes. The public-use data files contain data for all adolescents who have a completed household interview. Inclusion criteria for this study were (1) 15- to 17-year-old subjects in NIS-Teen 2017–2020 living in continental United States, (2) parent/guardian gave permission for NIS-Teen to contact their health care provider, (3) provider-reported HPV immunization history, and (4) provider-reported subject's age of first HPV vaccine was between 9 and 12 years. Finally, because reasons why children who initiated between the ages of 9 and 12 years had more than the recommended number of HPV vaccinations were not known, the specific dose for series completion could not be determined for those who had 4 to 6 HPV immunizations ($N = 340$); as such, analyses were further restricted to those whose providers reported the subject received no more than 3 doses of HPV vaccine. There were 19 575 adolescents in NIS-Teen 2017–2020 who met these 5 inclusion criteria to create the study sample.

Design

Figure 1 presents the study design along with key HPV vaccination program milestones. To create a retrospective cohort study from NIS-Teen 2017–2020, an accelerated longitudinal design approach was used. The accelerated longitudinal design uses a subject's age rather than study year to organize data into birth cohorts. Six birth cohorts (2000–2005) were developed from the 4 NIS-Teen study years to create a retrospective cohort study (See Supplemental Figure 3 and Supplemental Tables 5 and 6 for details).

Measures

Early Initiation

NIS-Teen includes several provider-reported measures of the age of first

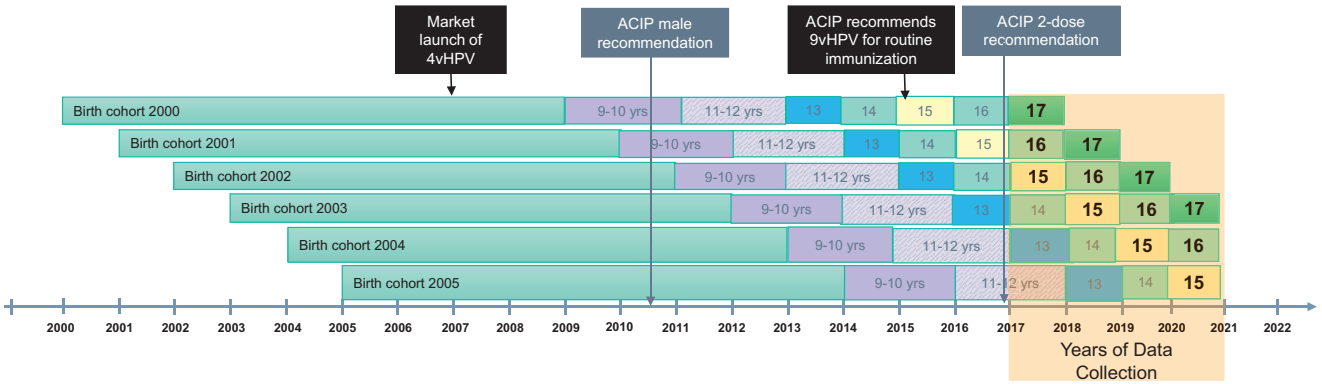

FIGURE 1
Accelerated longitudinal design using NIS-Teen years 2017–2020 to create a retrospective cohort study and HPV vaccination program timeline.

HPV vaccination (years, months, days). The age of HPV vaccination in years was dichotomized (9–10 years vs 11–12 years) to create the early initiation variable.

Outcome Measures

For all outcome measures, HPV series completion was determined per ACIP-recommended dose schedule. The HPV vaccine was initially approved as a 3-dose series. In 2016, ACIP recommended that those who initiated the vaccine at younger than age 15 years could receive a 2-dose schedule (0, 6–12 months). NIS-Teen includes a variable noting for those who initiated HPV vaccination before age 15 years if a subject had the requisite number of doses per ACIP guidelines and, for those with 2 doses, that there was an interval of at least 5 months, 4 days, between the first and second dose. As described in the following section, this NIS-Teen variable was used to derive the time and developmental pathway outcome variables for this study.

To assess the time pathway, 2 measures of HPV vaccination series completion were used: series completion by age 13 years (early adolescence) and series completion by age 15 years (mid-adolescence). We constructed a variable to denote the age of the last HPV vaccination received based on the total number of HPV vaccines and the age at which the final dose was received. Age at last HPV dose was set to the age of the second HPV vaccination for those who received 2 HPV vaccines and equal to the age at the third HPV vaccination for those who received 3 HPV vaccines. For series completion by ages 13 and 15 years, we constructed binary variables based on the NIS-Teen variable noted previously describing completion per ACIP recommended guidelines and the age of the last HPV vaccine received. Subjects who were up to date per ACIP guidelines and who received their last HPV vaccination before age 13 years were considered up to date by age 13 years. Likewise, subjects who completed before age 15 years were considered up to date by age 15 years.

To assess the development pathway, we constructed a binary variable to denote series completion within 3 years of initiation. The time interval between first and last HPV vaccination was calculated. Subjects were considered complete within 3 years if this interval was less than 3 years and the subject was complete per ACIP guidelines.

Covariates

Demographic, geographic, and provider covariates and their response categories from NIS-Teen included sex (female, male), race/ethnicity (non-Hispanic white, non-Hispanic Black, Hispanic, other, including other non-Hispanic race + multiple races), insurance status (private only, any Medicaid, other, uninsured), maternal education (less than 12 years, 12 years, greater than 12 year but less than college, college), Census region of residence (Northeast, Midwest, South, West), and type of facility where all of the subject's providers practiced (all private = private, all public = public, all hospital = hospital, all providers from a Special Supplemental Nutrition Program for Women, Infants, and Children clinic, school-based health center, pharmacy, military health care or other facility = school/other, and mixed/unknown). The NIS-Teen variable for income to poverty ratio was dichotomized at 1.5 to represent living in poverty (income to poverty ratio less than 150% or at least 150%). To assess urbanicity/rurality, 2010 US Census data were used.[9] The US Census defines an urbanized area as one with at least 50 000 people and a rural area as one with less than 2500 people. Data on the percent of the population living in urban and rural areas by state (and the District of Columbia) is available from the US Census (https://www.census.

gov/programs-surveys/geography/guidance/geo-areas/urban-rural/2010-urban-rural.html; accessed March 16, 2022). The distribution of percent of the population living in an urban area was explored and the cut point representing the top quintile determined. States with the percent of their population living in an urban area above the cut point ($N = 10$) were categorized as "urban." Similarly, distribution of percent of the population living in a rural area was explored and the cut point representing the top quintile determined. States with the percent of their population living in a rural area above that cut point ($N = 9$) were categorized as "rural." The state-based categorization of urban and rural were merged into the NIS-Teen data by matching to the state variable within NIS-Teen, which also includes the District of Columbia.

Data Analysis

Analyses were conducted using SPSS version 26. Sample weights were used only in regression analyses because this study is looking at correlates of completion rather than estimating vaccination coverage across years in the NIS sample, uses a select subset of NIS-Teen participants, and has created a retrospective cohort from multiple years of NIS-Teen data to take advantage of the provider-reported dates of vaccination. Descriptive statistics for the HPV measures and covariates were provided first. Next, bivariate contingency table analyses using Pearson χ^2 tests were performed to explore the associations between demographic, geographic, and provider variables and early initiation. An a priori level of significance of $\alpha < 0.05$ was set that, with Bonferroni adjustment led to $P < .0125$ to establish statistical significance. To determine if earlier age of initiation was an independent correlate of series completion, blocked stepwise logistic regression based on the literature and on bivariate analyses was performed. In step 0, a univariate model with just early initiation was run to determine the unadjusted odds ratio (OR) and 95% confidence intervals (CIs). Next, in step 1, a model without early initiation but including demographic, geographic, and provider covariates was run. Finally, early initiation was entered into the fully adjusted model to assess if early initiation was independently associated with time and development pathway outcomes and explore if early initiation influenced any disparities demonstrated in step 1. Adjusted ORs and 95% CIs are reported from both unweighted and weighted regression analyses.

To test the time pathway, this series of models was run separately for completion by age 13-year and completion by age 15-year outcomes. To test the development pathway, this series of models was run for the complete within 3-year outcome variables.

RESULTS

Table 1 describes the study population. More than one-half of these 19 575 adolescents were female (52.1%), non-Hispanic white (57.1%), or had private insurance only (57.3%). Early initiation was uncommon (7.5%). There was a more than twofold rise in series completion between the ages of 13 (34.5%) and 15 (83.4%) years. The majority (84.8%) were complete within 3 years.

Table 2 shows correlates of early initiation. All factors except living in a state with a high proportion living in an urban area were significantly associated with early initiation. Females were 1.5 times more likely to initiate at 9 to 10 years compared with males (8.9% vs 5.9%). Early initiation was also higher among socially disadvantaged populations, whether defined by race/ethnicity, socioeconomic status, or insurance. Geography was associated with early initiation: living in the South was associated with greater likelihood of early initiation, whereas living in a state with a high proportion living in a rural area decreased likelihood of early initiation. Early initiation was more common among those whose providers all practiced at public facilities or at school/other facilities compared with all hospitals, all private, or mixed/unknown facilities.

Table 3 shows demographic, geographic, and provider variables associated with the 3 measures of HPV vaccine series completion. Females were more likely to complete HPV vaccination by ages 13 and 15 years, but, although statistically significant, the magnitude of the differences were small. Completion within 3 years did not differ by sex. Table 3 reveals multiple disparities in series completion. Differences by Census region were found across the 3 outcomes, with the highest proportion completed in the Northeast for both time and the developmental pathway outcomes. Several markers of social disadvantage were also associated with lower likelihood of completion for all 3 outcome measures: non-Hispanic Black race/ethnicity, being uninsured, and having providers who all practiced in a public facility. However, lower maternal education was associated with increased likelihood of being up to date at age 13 years but decreased likelihood of being up to date at age 15 years or complete within 3 years compared with their peers with higher maternal education. Living in poverty was not associated with completion by age 13 years but was associated

TABLE 1 Description of the Population ($N = 19\,575$)

	Total		Female		Male	
	N	%	*N*	%	*N*	%
Sex[a]						
Male	9377	47.9	–	–	9377	100
Female	10 198	52.1	10 198	100	–	–
Birth cohort[b]						
2000	1071	5.5	666	6.5	405	4.3
2001	2787	14.2	1550	15.2	1237	13.2
2002	4580	23.4	2327	22.8	2253	24.0
2003	4958	25.3	2595	25.4	2363	25.2
2004	3932	20.1	1942	19.0	1990	21.2
2005	2247	11.5	1118	11.0	1129	12.0
Race/ethnicity[a]						
Non-Hispanic white	11 226	57.3	5858	57.4	5368	57.2
Non-Hispanic Black	1755	9.0	900	8.8	855	9.1
Hispanic	4318	22.1	2196	21.5	2122	22.6
Other[c]	2276	11.6	1244	12.2	1032	11.0
Census region[a]						
Northeast	3771	19.3	1941	19.0	1830	19.5
Midwest	4334	22.1	2233	21.9	2101	22.4
South	6980	35.7	3665	35.9	3315	35.4
West	4490	22.9	2359	23.1	2131	22.7
Insurance[a]						
Private only	10 658	54.6	5657	55.5	5028	53.6
Any Medicaid	6652	34.0	3362	33.0	3290	35.1
Other	1557	8.0	829	8.1	728	7.8
Uninsured	681	3.5	350	3.4	331	3.5
Maternal education[a]						
Less than 12 y	2510	12.8	1279	12.5	1231	13.1
12 y	3089	15.8	1601	15.7	1488	15.9
Some college	4913	25.1	2574	25.2	2339	24.9
College degree or higher	9063	46.3	4744	46.5	4319	46.1
Poverty[d]						
Income/poverty ratio $<$150%	5747	29.4	2915	28.6	2832	30.2
Income/poverty ratio $\geq$150%	13 828	70.6	7283	71.4	6545	69.8
Rural[e]						
Living in a top quintile rural state	3191	16.3	1651	16.2	1540	16.4
Not living in top quintile rural state	16 384	83.7	8547	83.8	7837	83.6
Urban[f]						
Living in top quintile urban state	3296	16.8	1726	16.9	1570	16.7
Not living in top quintile urban state	16 279	83.2	8472	83.1	7807	83.3
Facility[a]						
All private	8689	44.4	4554	44.7	4135	44.4
All public	2631	13.4	1322	13.0	1309	14.0
All hospital	2563	13.1	1344	13.2	1219	13.0
School/other	434	2.2	222	2.2	212	2.2
Mixed/unknown	5436	26.9	2856	27.0	2502	26.7
Age of initiation, y[g]						
9–10	1460	7.5	909	8.9	551	5.9
11–12	18 115	92.5	9289	91.1	8826	94.1
Series completion outcomes						
Time pathway						
Complete by age 13 y	6749	34.5	3709	36.4	3040	32.4
Complete by age 15 y	16 320	83.4	8588	84.2	7732	82.5
Development pathway						
Complete in 3 y	16 590	84.8	8679	85.1	7911	84.4

[a]Variable definition and categorization from NIS-Teen.

[b]Based on age at time of interview and year of data collection. Details found in Supplemental Tables 5 and 6.

[c]Other = other non-Hispanic race + multiple races. This category does not provide further specification in the NIS-Teen codebooks.

[d]Income to poverty ratio from NIS-Teen dichotomized at 1.5.

[e]Top quintile rural state based on the percent of the population living in a rural area from 2010 Census data with top quintile based on distribution across all 50 states and the District of Columbia.

[f]Top quintile urban state based on the percent of the population living in an urban area from 2010 Census data with top quintile based on distribution across all 50 states and the District of Columbia.

[g]Based on provider reported age of first HPV vaccination in years.

TABLE 2 Demographic, Geographic, and Provider Correlates of Early Initiation

	Total	Initiated 9-10 y		Initiated 11-12 y		
	N	*N*	%	*N*	%	Sig.[a]
Sex[b]						<.001
Female	10 198	909	8.9	9289	91.1	
Male	9377	551	5.9	8826	94.1	
Birth cohort[c]						<.001
2000	1071	87	8.1	984	91.9	
2001	2787	231	8.3	2556	91.7	
2002	4580	375	8.2	4205	91.8	
2003	4958	369	7.4	4589	92.6	
2004	3932	275	7.0	3657	93.0	
2005	2247	123	5.5	2124	94.5	
Race/ethnicity[b]						<.001
Non-Hispanic white	11 226	634	5.6	10 592	94.4	
Non-Hispanic Black	1755	180	10.3	1575	89.7	
Hispanic	4318	500	11.6	3818	88.4	
Other[d]	2276	146	6.4	2130	93.6	
Census region[b]						<.001
Northeast	3771	220	5.8	3551	94.2	
Midwest	4334	299	6.9	4035	93.1	
South	6980	615	8.8	6365	91.2	
West	4490	326	7.5	4164	92.7	
Insurance[b]						<.001
Private only	10 658	576	5.4	10 109	94.6	
Any Medicaid	6652	684	10.3	5968	89.7	
Other	1557	136	8.7	1421	91.3	
Uninsured	681	64	9.4	617	90.6	
Maternal education[b]						<.001
Less than 12 y	2510	306	12.2	2204	87.8	
12 y	3089	307	9.9	2782	90.1	
Some college	4913	366	7.4	4547	92.6	
College degree or higher	9063	481	5.3	8582	94.7	
Poverty[e]						<.001
Income/poverty ratio <150%	5747	655	11.4	5092	88.6	
Income/poverty ratio >150%	13 828	805	5.8	13 023	94.2	
Rural[f]						.010
Living in a top quintile rural state	3191	203	6.4	2988	93.6	
Not living in top quintile rural state	16 384	1257	7.7	15 127	93.2	
Urban[g]						NS[h]
Living in top quintile urban state	3296	245	7.4	3051	92.6	
Not living in top quintile urban state	16 279	1215	7.5	15 064	92.5	
Facility[b]						<.001
All private	8689	602	6.9	8087	93.1	
All public	2631	245	9.3	2386	90.7	
All hospital	2563	174	6.8	2389	93.2	
School/other	434	49	11.3	385	88.7	
Mixed/unknown	5436	390	7.4	4868	92.6	

NS, not significant.

[a]Significance based on Pearson χ^2 tests with statistical significance level set at $P < .0125$.

[b]Variable definition and categorization from NIS-Teen.

[c]Based on age at time of interview and year of data collection. Details found in Supplemental Tables 5 and 6.

[d]Other = other non-Hispanic race + multiple races. This category does not provide further specification in the NIS-Teen codebooks.

[e]Income to poverty ratio from NIS-Teen dichotomized at 1.5.

[f]Top quintile rural state based on the percent of the population living in a rural area from 2010 Census data with top quintile based on distribution across all 50 states and the District of Columbia.

[g]Top quintile urban state based on the percent of the population living in an urban area from 2010 Census data with top quintile based on distribution across all 50 states and the District of Columbia.

with the other 2 outcome measures. Although statistically significant, in each case, the magnitude of the disparities was small.

Bivariate analyses suggested that early initiation worked through both the time and development pathways, but in the opposite direction (Fig 2).

For the time pathway, early initiators were 2.4 times more likely to complete the series by age 13 years compared with those who

TABLE 3 Demographic, Geographic, and Provider Correlates of Different Measures of HPV Series Completion

	Time Pathway						Development Pathway		
	Complete by Age 13 y			Complete by Age 15 y			Complete Within 3 y		
	N	%	Sig	*N*	%	Sig	*N*	%	Sig[a]
Sex[b]			<.001			<.001			NS
Female	3709	36.4		8588	84.2		8679	85.1	
Male	3040	32.4		7732	82.5		7911	84.4	
Birth cohort[c]			<.001			<.001			<.001
2000	283	41.2		815	76.1		867	81.0	
2001	1766	40.5		2149	77.1		2275	81.6	
2002	1368	41.2		3714	81.1		3801	83.0	
2003	1606	41.7		4258	85.9		4263	86.0	
2004	1578	40.8		3393	86.3		3399	86.4	
2005	1148	51.1		1991	88.6		1985	88.3	
Race/ethnicity[b]			<.001			<.001			<.001
Non-Hispanic white	3715	33.1		9456	84.2		9638	85.9	
Non-Hispanic Black	559	31.9		1421	81.0		1443	82.2	
Hispanic	1677	38.8		3517	81.4		3549	82.2	
Other[d]	798	35.1		1926	84.6		1960	86.1	
Census region[b]			.003			<.001			<.001
Northeast	1279	33.9		3404	90.3		3486	92.4	
Midwest	1459	33.7		3651	84.2		3726	86.0	
South	2524	36.2		5620	80.5		5681	81.4	
West	1487	33.1		3645	81.2		3697	82.3	
Insurance[b]			<.001			<.001			<.001
Private only	3579	33.5		9115	85.3		9311	87.1	
Any Medicaid	2417	36.3		5464	82.1		5503	82.7	
Other	547	35.1		1257	80.7		1282	82.3	
Uninsured	206	30.2		484	71.1		494	72.5	
Maternal education[b]			<.001			<.001			<.001
Less than 12 y	980	39.0		2031	80.9		2044	81.4	
12 y	1108	35.9		2505	81.1		2516	81.5	
Some college	1590	32.4		3955	80.5		4012	81.7	
College degree or higher	3071	33.9		7829	86.4		8018	88.5	
Poverty[e]			NS			<.001			<.001
Income/poverty ratio <150%	2053	35.7		4625	80.5		4668	81.2	
Income/poverty ratio ≥150%	4696	34.0		11 695	84.6		11 922	86.2	
Rural[f]			NS			<.001			.012
Living in a top quintile rural state	1091	34.2		2596	81.4		2633	82.5	
Not living in top quintile rural state	5658	34.5		13 724	83.8		13 957	85.2	
Urban[g]			<.001			NS[h]			.004
Living in top quintile urban state	1047	31.8		2782	84.4		2847	86.4	
Not living in top quintile urban state	5702	35.0		13 538	83.2		13 743	84.4	
Facility[b]			.042			<.001			<.001
All private	3042	35.0		7448	85.7		7586	87.3	
All public	839	31.9		2015	76.6		2022	76.9	
All hospital	885	34.5		2221	86.7		2267	88.5	
School/other	159	36.6		341	78.6		347	80.0	
Mixed/unknown	1824	34.7		4295	81.7		4368	83.1	

NS, not significant.

[a]Significance based on Pearson χ^2 tests with statistical significance level set at $P < .0125$.

[b]Variable definition and categorization from NIS-Teen.

[c]Based on age at time of interview and year of data collection. Details found in Supplemental Tables 5 and 6.

[d]Other = other non-Hispanic race + multiple races. This category does not provide further specification in the NIS-Teen codebooks.

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[f]Top quintile rural state based on the percent of the population living in a rural area from 2010 Census data with top quintile based on distribution across all 50 states and the District of Columbia.

[g]Top quintile urban state based on the percent of the population living in an urban area from 2010 Census data with top quintile based on distribution across all 50 states and the District of Columbia.

initiated HPV vaccination at 11 to 12 years (74.0% vs 31.3%; $P < .001$). This difference was maintained at age 15 years, although decreased in magnitude to a 1.1-fold difference (91.7% vs 84.9%; $P < .001$). In contrast, looking at the development pathway, early initiation was

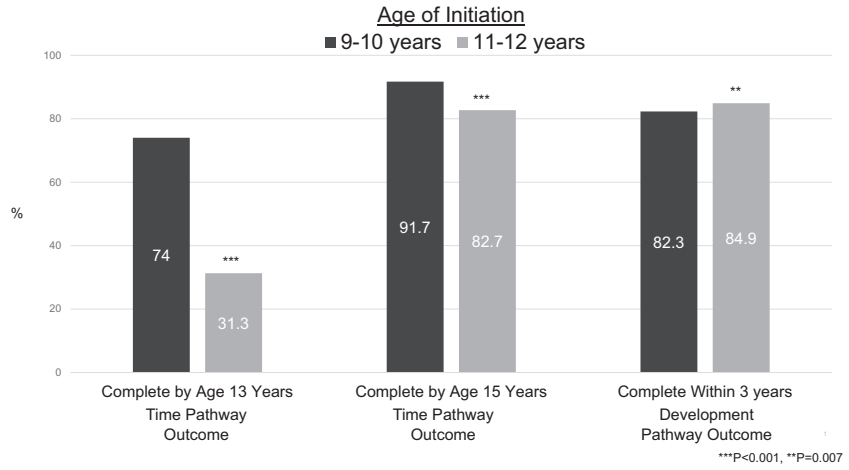

FIGURE 2
Bivariate analyses of early initiation and HPV series completion time and development pathway outcomes.

associated with a slightly lower likelihood of completion within 3 years (82.3% vs 84.9%; $P = .007$).

Multivariable logistic regression modeling demonstrated that the association of early initiation was independent of other correlates of series completion for time pathway outcomes (Table 4). However, early initiation was not an independent predictor for the development pathway outcome in unweighted analyses and had a negligible association in weighted analyses. Furthermore, logistic regression modeling did not suggest that early initiation altered sociodemographic, geographic, or provider-based disparities in series completion (see Supplemental Table 7 for details).

DISCUSSION

This retrospective study, which takes advantage of provider reported vaccination data in NIS-Teen, assessed HPV series completion in early and mid-adolescence among 15 to 17 year olds spanning 6 birth cohorts and explored pathways by which early initiation might influence completion. We demonstrated that early initiation was a strong predictor of completion at both ages 13 and 15 years but that 9- to 10-year-old initiators were no more likely to complete vaccination within 3 years than their counterparts who initiated vaccination at ages 11 to 12 years. These findings suggest that, by increasing the available time between initiation and target completion age, early initiation gives providers more touch points and therefore more opportunities to complete the series. The idea that early initiation could increase completion because the vaccine was given at an earlier developmental period was not supported, nor do our findings suggest that early initiation alters disparities in HPV series completion.

HPV immunization is most effective if given before sexual debut. In the United States, since the late 1990s, sexual activity rates have been relatively constant: 7% report sexual debut by age 13, and 30% of females and 34% of males are sexually active by age 16 years.[10] Given the more than fourfold rise in initiation of sexual activity between ages 13 and 16 years, improving HPV series completion by the younger age of 13 years would have important public health benefits. Our findings indicate that moving routine HPV vaccination from age 11 to 12 years, the current ACIP

TABLE 4 Multivariable Modeling of the Association of Early Initiation to Time and Development Pathway Measures of HPV Series Completion

	Univariate Model		Multivariable Model	
Measure of Series Completion	Early Initiation Unadjusted OR	95% CIs	Early Initiation Adjusted OR	95% CIs
Unweighted analyses				
Time pathway				
Complete by age 13 y	6.24	5.53–7.04	6.68	5.90–7.56
Complete by age 15 y	2.32	1.91–2.80	2.66	2.20–3.23
Development pathway				
Complete within 3 y	0.83	0.72–0.95	0.94	0.81–1.08
Weighted analyses				
Time pathway				
Complete by age 13 y	6.92	6.90–6.95	7.68	7.65–7.71
Complete by age 15 y	2.37	2.36–2.38	2.65	2.64–2.67
Development pathway				
Complete within 3 y	0.94	0.93–0.94	1.02	1.018–1.027

Note: Multivariable models adjust for sex (female = ref), birth cohort (2000 = ref), race/ethnicity (non-Hispanic white = ref), Census region (Northeast = ref), insurance status (private = ref), maternal education (college = ref), rural (nonrural = ref), urban (nonurban = ref), facility (private = ref), poverty (income/poverty ratio at least 150% = ref). See supplementary file 2 for details.

recommended age, to age 9 to 10 years would improve coverage by age 13 years, thereby providing greater population-level protection from HPV-related disease.

Early initiation was uncommon and the reasons underlying early initiation in the 7.5% who did initiate at ages 9 to 10 years are unknown. However, our findings that early initiation was more common in females, non-Hispanic Black and Hispanic populations, and lower socioeconomic status teens may provide clues as to 1 potential factor underlying why these children initiated HPV vaccination before the current ACIP recommended ages. These factors are all associated with earlier entry into puberty. Girls enter into puberty about 1.5 years earlier than boys and markers of social disadvantage have been linked to pubertal timing.[11] At age 9 years, 62.6% of non-Hispanic Blacks have breast and pubic hair development at Tanner stage 2 compared with 32.1% of non-Hispanic whites for breast development and 20.0% for pubic hair.[12] Median age of menarche, which occurs late in puberty, is also earlier in non-Hispanic Black (12.06) and Hispanic (12.25) girls compared with non-Hispanic white girls (12.55).[13] Socioeconomic disadvantage has increased the rate of early puberty fourfold in boys and twofold in girls.[11] Providers may have recommended early HPV vaccination for early maturing patients, especially because early puberty is associated with increased sexual risk behaviors.[14] Provider concern of the higher rates of cervical cancer among non-Hispanic Black and Hispanic women and practice patterns are other potential provider-related factors that may have led to the recommendation to initiate HPV vaccination at ages 9 to 10 years. Parental factors such as parental health seeking behaviors and attitudes toward vaccines in general and HPV-related knowledge could also influence early initiation. Further research is needed to assess this hypothesis and to understand both provider and parental reasons for early initiation.

Most adolescents in this study received a 3-dose series of HPV vaccine for completion. In late 2016, ACIP changed the dose recommendation from 3 to 2 for those who initiate vaccination before age 15 years.[15] The impact of the change in recommended doses on vaccination coverage rates remains to be determined, but it is expected that fewer required doses would improve completion. In this retrospective study, we explore if early initiation affected series completion and found that early initiation was associated with increased completion at both ages 13 and 15 years. Further research will need to confirm our findings, particularly in this era of a 2-dose recommendation. Future research will also be needed to understand the acceptability and impact of moving the active recommendation for initiation of HPV vaccination to ages 9 to 10 years.

This study has several limitations. We assigned birth cohorts based on age at interview and survey year because date of birth was not available in the public-use data. This likely led to some misclassification of the birth cohort variable in that an individual interviewed before his or her birthday in any calendar year would be assigned to a 1-year younger birth cohort. However, any misclassification is distributed across all birth cohorts. Because this variable is used only as a marker for time in the study, such misclassification is likely to have minimal impact. Indeed, findings did not change in multivariable logistic regression analyses run without the birth cohort variable. As noted, reasons for offering early initiation and whether initiation was requested by the parent or recommended by the provider are unknown. Although national in scope, this study should not be considered nationally representative. Provider report of vaccination status relied on parental consent to contact providers and that those providers respond to the NIS-Teen questionnaire, both of which could introduce bias. Furthermore, this convenience sample constructed with only a subset of NIS-Teen subjects with adequate provider data through use of an accelerated longitudinal design, was not consistent with use of NIS-Teen sample weights throughout. Our urban/rural measure, although derived from Census data, was state-based and therefore not specific to area of residence. Balancing these limitations are the study's significant strengths: the creative design, use of provider-reported HPV vaccination, careful attention to dose requirement, and novel exploration of the time and development pathways.

CONCLUSION

In conclusion, this study provides evidence that moving routine HPV vaccination from ages 11 to 12 years to ages 9 to 10 years may improve vaccination coverage rates in early and mid-adolescence, thereby increasing the public health benefit of vaccination. Providers should be vigilant to patient interactions after initiation of HPV vaccination to ensure series completion within the recommended time frame. Future research on acceptability of and barriers to routine vaccination at ages 9 to 10 years could promote uptake and completion before sexual debut, thereby maximizing HPV vaccine effectiveness.

ABBREVIATIONS

ACIP: Advisory Committee on Immunization Practices
CI: confidence interval
HPV: human papillomavirus
NIS: national immunization surveys
OR: odds ratio

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