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Impact of introduction of the 9-valent human papillomavirus vaccine on vaccination coverage of youth in North Carolina

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ABSTRACT

Objectives: The objective of this study was to evaluate the impact of introduction of 9vHPV vaccine on HPV vaccination uptake (doses per capita) and initiation (≥1 doses), completion (≥3 doses) and compliance (≥3 doses within 12 months) by adolescents.
Methods: We used a retrospective cohort analysis using North Carolina Immunization Registry (NCIR) data from January 2008 through October 2016. The sample included Vaccines for Children eligible adolescents aged 9 to 17 years in 2016, for whom the NCIR contains complete vaccination history. We applied an interrupted time series design to measure associations between ZIP Code Tabulation Area (ZCTA)-level HPV vaccination outcomes over time with the introduction of 9vHPV in North Carolina (NC) in July 2015.
Results: Each outcome displayed a linear upward trend over time with large seasonal spikes near August of each year, corresponding to the time when adolescents often receive other vaccines required for school entry. After accounting for these underlying trends, introduction of 9vHPV was not associated with a change in publicly funded HPV vaccination rates in NC.
Conclusions: Our results indicate that 9vHPV substituted for 4vHPV in the first year after release in NC, but the release of 9vHPV was not associated with an overall change in HPV vaccination.

1. Introduction

Human papillomavirus (HPV) is the most common sexually-transmitted infection in the United States (US), causes genital warts, and is associated with cervical, vaginal, vulvar, anal, penile, and throat cancers [1]. In 2007 the US Advisory Committee on Immunization Practices (ACIP) began recommending a three-dose HPV vaccination for all girls. The routinely recommended age is 11 to 12 years, but the vaccine can be given as young as 9 years with catch-up vaccination recommended for females aged 13 to 26 years who have not been previously vaccinated. After providing permissive recommendations for males in 2009 for the prevention of genital warts, males were included in the routine recommendation for vaccination in 2011 due to a new vaccine indication for the prevention of anal cancer. The routine recommended age for males is 11 to 12 years, but the vaccine can be given as young as 9 years with catch-up vaccination recommended for males aged 13 to 21 years who have not been previously vaccinated [2]. Vaccination is also recommended for men who have sex with men through age 26 years and for immunocompromised persons (including those with HIV infection). It may be given to males age 22–26 years.

There are three types of HPV vaccines licensed in the US. A bivalent HPV vaccine is indicated for females only and prevents infection with HPV types 16 and 18. A quadrivalent HPV vaccine (4vHPV) is indicated for use among both females and males and protects against HPV types 6, 11, 16 and 18. In December 2014, the Food and Drug Administration approved a 9-valent HPV vaccine (9vHPV; Gardasil 9, Merck and Co., Inc.) that adds protection against HPV types 31, 33, 45, 52 and 58 to the 4vHPV vaccine. 9vHPV was added to the ACIP recommendation in February 2015 [4]. By the end of 2016, only the 9vHPV vaccine was commercially available in the US.

Despite effective, recommended vaccines [5–9], HPV vaccination coverage is far below the national objective (80%) set by

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Healthy People 2020. In 2015 in the United States, completion of the three-dose series among ages 13 to 17 was only 42% for girls and 28% for boys [10]. The parallel figures for North Carolina were 37.8% for females and 29.8% for males [10]. In comparison, national completion rates for Tdap and MCV4 were 86% and 81%, respectively [10].

Currently, little is known about the impact this transition may have on population coverage rates. The objective of this study is to evaluate the impact of introduction of the 9vHPV vaccine on area-level estimates of HPV vaccination uptake, initiation, completion and compliance.

2. Methods

2.1. Design

We used a retrospective cohort from the North Carolina Immunization Registry (NCIR) to evaluate HPV vaccine utilization. The 9vHPV vaccine was first distributed by the North Carolina (NC) Department of Health and Human Services beginning on July 1st, 2015. We used an interrupted time series design that compared area-level HPV vaccination rates before and after the introduction of 9vHPV (i.e., July 2015) while accounting for seasonal and other time series trends in the data. We used this design because it does not require a comparison group (i.e., an area that did not have access to 9vHPV). Because 9vHPVwas made available statewide in the same month, there is no natural comparison group.

2.2. Data

The NCIR is a secure, web-based clinical tool to provide official immunization information to the state [12]. The registry's primary users are local health departments (100% participate), private provider offices that receive vaccines from the federally funded Vaccines for Children (VFC) program (over 90% of offices that receive VFC vaccines participate), and clinics associated with the state's medical schools. VFC provides vaccines at no cost to adolescents who otherwise might not be vaccinated because of their parent or guardian's inability to pay. Health care providers who receive VFC vaccines are required to document administration of those vaccines in the NCIR (approximately 95%) or via an alternative hard copy form (approximately 5% that are not captured in the NCIR). The NCIR provided information on receipt of HPV vaccinations, date of receipt, type of HPV vaccine, sex, race, Hispanic ethnicity, and ZIP code.

We mapped ZIP codes to ZIP Code Tabulation Areas (ZCTAs) using a crosswalk created by a Health Resources and Services Administration-funded project directed by the Robert Graham Center [13]. ZCTAs are generalized area representations of ZIP code service areas developed by the U.S. Census Bureau to overcome the difficulties in precisely defining the land area covered by each ZIP code. The crosswalk lists all ZIP codes included in each ZCTA. We collected geographic boundary and demographic characteristics for all North Carolina ZCTAs from the U.S. Census Bureau using the 2013 TIGER shape files, 2010 U.S. Census, and 2010–2014 (5 year) American Community Survey (ACS). We also collected county-level characteristics from the 2014–2015 Area Resource File (ARF) and 2008–2014 County Business Patterns (CBP), using the TIGER shape files to crosswalk from county to ZCTA.

2.3. Sample

We identified age-eligible adolescents from the NCIR starting in January 2008 and running through October 2016. October 2016 provides over one year of data after the introduction of 9vHPV in NC and also captures the peak summer vaccination season in 2016. To ensure complete records for adolescents in the registry, our analytic sample included adolescents who turned nine years old between January 2008 and October 2016. Thus, our sample included adolescents between the ages of nine, the youngest age at which the HPV vaccination can be given, and 17 years in 2016 (i.e., adolescents who were nine years old in 2008). The NCIR contains complete vaccination history, including date of administration and type of HPV vaccine, for this cohort of adolescents, the oldest of which were nine in 2008. By definition, all adolescents in the analysis cohort were vaccine naïve prior to entry and initiated the series during the study period. We excluded adolescents in the NCIR with missing values for date of the HPV vaccine, HPV vaccine type, sex or ZIP code (Table 1).

2.4. Dependent variables

Four outcomes were assessed in the study: uptake, initiation, completion, and compliance. All outcomes were calculated using publicly funded vaccinations as rates per ZCTA/month/year and were stratified by sex. Vaccine uptake was characterized as the number of publicly funded HPV doses per capita in the age-eligible (ages 9 to 17) population. Vaccine initiation was assessed among those who were eligible to receive the HPV vaccine and characterized as the proportion of VFC-eligible adolescents ages 9 to 17 (i.e., uninsured and means-tested, publicly insured adolescents) who had received an initial dose of HPV vaccine during the relevant time period. Vaccine completion was characterized as the proportion of VFC-eligible adolescents (ages 9–17) who completed three or more doses. Vaccine compliance was initially characterized as the proportion of adolescents who completed doses 2 and 3 with appropriate dose spacing as in the ACIP recommended schedule shown in Fig. 1. We relaxed the definition of compliance to include adolescents receiving their third dose within one year of their first dose due to very low compliance rates when using the ACIP recommended schedule.

We used VFC-eligible adolescents ages 9 to 17 (i.e., uninsured and means-tested, publicly insured adolescents) from the 2010 Census as the denominator. These publicly available data were merged by ZCTA to our aggregated NCIR data set. Because the NCIR reporting is not as complete for higher income adolescents, who may receive private insured stocked vaccine that is not required to be entered into NCIR, VFC-eligible adolescents was the population most fully covered in the NCIR. In sensitivity analysis, we used the full population of adolescents ages 9 to 17 as the denominator and included privately funded doses in the numerator for all outcomes.

Table 1
Inclusion and exclusion criteria for NCIR vaccination counts.

	Dropped		Remaining
	N	%	
Original person and person-dose observations			3,813,416
Excluded those with missing gender	150,965	4.0%	3,662,451
Excluded those with missing ZIP code	858,490	23.4%	2,803,961
Excluded those whose birthdate is out of range	1,206,154	43.0%	1,597,807
Excluded those whose age at immunization is <9	547	0.03%	1,597,260
Excluded person-only records [no HPV vaccination given]	748,543	46.9%	848,717
Excluded those with missing vaccine type	4832	0.6%	843,885
Excluded those whose ZIP code does not map to a North Carolina ZCTA	11,483	1.4%	832,402
Excluded non-publicly funded doses	378,485	45.5%	**453,917**