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Younger age at initiation of the human papillomavirus (HPV) vaccination series is associated with higher rates of on-time completion

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ABSTRACT

Vaccination rates for human papillomavirus (HPV) have remained disappointingly low. It is critical to identify methods to increase on-time vaccine series completion rates (before 13 or 15 years). To determine whether younger age (9 to 10 years of age) at HPV vaccine series initiation was associated with improved on-time completion rates compared to initiation at 11 to 12 years, we examined the prevalence of on-time HPV vaccine series completion rates from August 2006 through December 2012 in a large, population-based cohort of children and adolescents (aged 9.5 to 27 years) residing in Olmsted County, MN on December 31, 2012 ($n = 36,223$). We compared age at vaccine initiation between individuals who successfully completed both 2 and 3 doses of the vaccination series on-time (before age 13.5 or 15.0 years) using multivariate logistic regression. On-time completion of both 2 and 3 doses of the vaccine series by age 13.5 or 15.0 years was significantly associated with initiation at 9 to 10 years as compared to 11 to 12 years after adjusting for sex, race, insurance status, frequent health care visits, and year of first vaccination (all $p < .01$). Interventions focused on beginning the vaccination series at 9 to 10 years of age may result in higher rates of timely series completion.

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1. Introduction

Human papillomavirus (HPV) is the most common sexually transmitted disease, with about 14 million incident HPV cases each year, (Centers for Disease Control and Prevention, 2012) and an overall prevalence of approximately 43% among women 14 to 59 years of age (Hariri et al., 2011). While infection with HPV is asymptomatic, HPV can cause cervical cancer as well as many other anogenital and oropharyngeal cancers (Chaturvedi et al., 2011; Jayaprakash et al., 2011; Lowy et al., 2008). More than 33,000 new cases of HPV-caused cancers occur in the United States (US) each year (Centers for Disease Control and Prevention, 2012).

The US Food and Drug Administration has licensed three HPV vaccines, the first two with high efficacy against the two strains of HPV that cause about 70% of cervical cancers (Gardasil® and Cervarix®) (Munoz et al., 2004; Schiffman et al., 2007). The third nonavalent vaccine received approval in December 2014 (Gardasil®9) and could potentially prevent 90% of cervical cancers (Joura et al., 2015).

Completion of the vaccine series prior to initiation of sexual activity is crucial for prevention of cervical cancers, since the vaccine is most effective in persons not previously exposed to HPV (Herrero et al., 2011; Markowitz et al., 2014). Therefore, Healthy People 2020 has set a target for an 80% completion rate of the 3-dose HPV vaccine series for girls/women by 13 to 15 years of age (Centers for Disease Control and Prevention, 2012). The rate of vaccine uptake has increased over time; however, the 2014 National Immunization Survey showed that only 39.7% of girls aged 13–17 years had completed the series (Reagan-Steiner et al., 2015). In addition, only 21.6% of boys of the same age had completed the 3-dose series (Reagan-Steiner et al., 2015).

The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination at 11 to 12 years of age but gives permission for use of the HPV vaccine beginning at 9 years of age (Markowitz et al., 2014). Several studies indicate that earlier age at vaccination is associated with a stronger immune response, (Block et al., 2006; Giuliano et al., 2007; Reisinger et al., 2007) and the duration of protection of the HPV vaccines is known to be at least 8 to 9 years, with little evidence of waning immunity (Ferris et al., 2014; Naud et al., 2014). Therefore, vaccination at earlier ages would still confer protection throughout adolescence and early adulthood. Furthermore, earlier initiation of the vaccine offers more time for completion of the series by the

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recommended ages. Earlier initiation of the vaccine could therefore offer the dual benefit of improved immunity and higher completion rates. It is unclear, however, whether younger age at initiation is associated with higher on-time completion rates of the vaccine series. We therefore hypothesized that initiating the HPV vaccine series at 9 to 10 years of age would be associated with a higher rate of on-time completion of the 3-dose vaccine series compared to initiating the series at 11 to 12 years.

Finally, persistently poor HPV vaccine series completion rates by 13 to 15 years have prompted several studies examining the efficacy of a 2-dose, rather than a 3-dose series. Two doses of the HPV vaccine produce a non-inferior antibody response in healthy girls aged 9–14 years compared to three doses (D'Addario et al., 2014). These findings form the basis of the current World Health Organization recommendations for completion of two doses of HPV vaccine among girls 9–13 years of age (World Health Organization, 2015).

Although the United States has not yet adopted a 2-dose HPV vaccination policy, we also examined the association between age at vaccine initiation and on-time completion of two doses of the vaccine as a secondary outcome.

2. Methods

2.1. Study design and population

We used the Rochester Epidemiology Project (REP) to identify all children and adolescents who were 9.5 to 27 years of age and residing in Olmsted County, Minnesota (MN) on December 31, 2012. Only those ages 9.5 and older (up to 27 years of age) on December 31, 2012 were included in the cohort, as younger children would not have had the opportunity to complete all three doses by December 31, 2012. Briefly, the REP links data on medical care delivered to the population of Olmsted County, MN. Primary care in this community is currently provided by a limited number of health care practitioners. These practitioners share their medical record information through the REP research infrastructure for approved research studies (St Sauver et al., 2011, 2012). The dates of the health care visits to any of these practitioners are linked to addresses at the time of the visit, and this information is used to define who resided in Olmsted County at any given point in time since 1966 (REP Census). The population counts obtained by the REP Census are similar to those obtained by the US Census, indicating that virtually the entire population of the county is captured by the system (St Sauver et al., 2011). We included in our analyses only those individuals who had given permission for their medical records to be used for research, and this study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

2.2. Identification of vaccines

We searched the REP electronic data to identify all HPV vaccinations received by the study population between August 2, 2006 and December 31, 2012, using the current procedural terminology (CPT) codes 90649 (Gardasil®) and 90650 (Cervarix). Gardasil®9 was not included in this study, because it was not available to this population during the study time frame.

In 2006, some of the health care practitioners in the study region began offering HPV vaccination at 9 to 10 years of age. However, because only some of the health care practitioners changed their practices, most children in the region continued to be eligible for the vaccine only at ages 11 to 12 years. This natural experiment made it possible for us to compare the on-time vaccination completion rates between children initiating the series at different ages. Children and adolescents were defined as having completed the series if they had received three doses of the HPV vaccine with appropriate spacing by December 31, 2012. Appropriate spacing was defined according to recommendations from ACIP (Centers for Disease Control and Prevention, 2010a,b). The

second dose must have been administered at least 4 weeks (24 days) after the first dose. The third dose must have been administered at least 12 weeks (80 days) after the second dose, and at least 24 weeks (164 days) after the first dose (Markowitz et al., 2014). A 4-day grace period was permitted at each dose (Centers for Disease Control and Prevention, 2011). We excluded doses given before 9 years of age ($n = 7$) except for those who received the first dose within 4 days of their 9th birthday ($n = 5$) in accordance with the ACIP General Recommendations on Immunizations regarding minimal intervals and grace periods (Centers for Disease Control and Prevention, 2011). Children were classified as having completed either 2 doses or the full 3-dose series on-time (by the recommended ages) or not on time.

2.3. Analysis

Characteristics of the study population were described overall, including the proportion of the population that had completed either 2 or 3 doses of the vaccine with appropriate spacing. The population was sub-set to those that had completed either 2 or 3 doses of the vaccine. Timely (or on-time) completion of the series was defined as completion of the vaccine by 13.5 or 15 years. Age 13.5 years was used to allow children who were almost 13 years old at time of initiation to complete the vaccine series within the recommended 6-month window. For example, if a child initiated the series at 12 years, 11 months, it would not be possible to complete the series by age 13.0 years, but the 6 month grace period would allow for completion. Timely completion of the series by age 15 was also assessed in accordance with Healthy People 2020 recommendations (Centers for Disease Control and Prevention, 2011). A grace period was not applied to completion by age 15 because anyone who initiated the vaccine series prior to age 13 would have ample time to complete the series by age 15.

Sex, race, insurance status, high frequency of health care visits, year of series initiation, and proportion completing the series by 13.5 or

Table 1

Characteristics of children and adolescents 9.5 to 27 years of age residing in Olmsted County, MN on December 31, 2012.

Characteristic	N = 36,223
Sex	
Boys/Men	16,906 (46.7)
Girls/Women	19,317 (53.3)
Age as of 12/31/2012 (years)	
9.5–<11	2912 (8.0)
≥11–<13	3648 (10.1)
≥13–<16	5434 (15.0)
≥16–<22	11,316 (31.2)
≥22–<27	10,635 (29.4)
27	2278 (6.3)
Race	
White	28,268 (78.0)
Asian	1706 (4.7)
Black or African American	2388 (6.6)
Other or unknown	3861 (10.7)
Insurance status ^a	
No/unknown	6437 (17.8)
Commercial	22,921 (63.3)
Government	4589 (12.7)
Other	2276 (6.3)
Completion of 2 doses of the HPV vaccine ^b	9283 (25.6)
Duration between first and second dose (months), median (IQR) ^c	2.7 (2.1, 5.4)
Completion of 3 doses of the HPV vaccine ^b	6989 (19.3)
Duration between first and third dose (months), median (IQR) ^c	2.5 (2.1, 4.5)

Abbreviations: IQR, interquartile range. Results presented as N (%) unless otherwise noted.

^a Insurance status closest to August 2, 2006.

^b Receipt of doses with appropriate timing (The second dose must have been administered at least 4 weeks (24 days) after the first dose. The third dose must have been administered at least 12 weeks (80 days) after the second dose, and at least 24 weeks (164 days) after the first dose. A 4-day grace period was permitted at each dose.)

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